KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION, MANAGEMENT, AND TREATMENT OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

CONFIDENTIAL: DO NOT DISTRIBUTE

PUBLIC REVIEW DRAFT
October 2023
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FHKAM
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Marcello A. Tonelli, MD, SM, MSc, FRCPC
Wolfgang C. Winkelmayer, MD, MPH, ScD

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Coral Cyzewski, Events Coordinator
Kathleen Conn, Director of Communications
REFERENCE KEYS

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the certainty of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>Most people in your situation would want the recommended course of action, and only a small proportion would not.</td>
<td>The recommendation can be evaluated as a candidate for developing a policy or a performance measure.</td>
</tr>
<tr>
<td>“We recommend”</td>
<td>Most patients should receive the recommended course of action.</td>
<td></td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>The majority of people in your situation would want the recommended course of action, but many would not.</td>
<td>The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.</td>
</tr>
<tr>
<td>“We suggest”</td>
<td>Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Certainty of evidence</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect is close to the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimate of effect is very uncertain, and often it will be far from the true effect.</td>
</tr>
</tbody>
</table>
**CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO**

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1-G5), and Albuminuria category (A1-A3), abbreviated as CGA.

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
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<tbody>
<tr>
<td>Description and range</td>
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<td></td>
<td></td>
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<tr>
<td>Normal to mildly increased</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moderately increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severely increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 mg/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 mg/mmol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–300 mg/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–30 mg/mmol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 300 mg/g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30 mg/mmol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

- **G1**: Normal or high
  - GFR: Normal or high
  - Albuminuria: ≥ 90
  - Color: Green
- **G2**: Mildly decreased
  - GFR: 60–89
  - Albuminuria: Not specified
  - Color: Yellow
- **G3a**: Mildly to moderately decreased
  - GFR: 45–59
  - Albuminuria: Not specified
  - Color: Orange
- **G3b**: Moderately to severely decreased
  - GFR: 30–44
  - Albuminuria: Not specified
  - Color: Red
- **G4**: Severely decreased
  - GFR: 15–29
  - Albuminuria: Not specified
  - Color: Red
- **G5**: Kidney failure
  - GFR: < 15
  - Albuminuria: Not specified
  - Color: Red

Green, low risk (if no other marker of kidney disease, no CKD); Yellow, moderately increased risk; Orange, high risk; Red, very high risk. GFR; glomerular filtration rate.
### CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

<table>
<thead>
<tr>
<th>Conventional unit</th>
<th>Conversion factor</th>
<th>SI Unit</th>
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<tbody>
<tr>
<td>ACR mg/g</td>
<td>0.113</td>
<td>mg/mmol</td>
</tr>
<tr>
<td>Creatinine mg/dl</td>
<td>88.4</td>
<td>µmol/l</td>
</tr>
<tr>
<td>PCR mg/dl</td>
<td>0.113</td>
<td>mg/mmol</td>
</tr>
</tbody>
</table>

Note: Conventional unit x conversion factor = SI unit

### EQUIVALENT ALBUMINURIA CATEGORIES IN CKD

<table>
<thead>
<tr>
<th>Category</th>
<th>AER (mg/24 hours)</th>
<th>ACR (approximate equivalent)</th>
<th>Terms</th>
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</thead>
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<tr>
<td>A1</td>
<td>&lt;30</td>
<td>&lt;3</td>
<td>&lt;30</td>
</tr>
<tr>
<td>A2</td>
<td>30-300</td>
<td>3-30</td>
<td>30-300</td>
</tr>
<tr>
<td>A3</td>
<td>&gt;300</td>
<td>&gt;30</td>
<td>&gt;300</td>
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</table>

*Relative to young adult level

ACR, albumin-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AAA</td>
<td>abdominal aortic aneurysm</td>
</tr>
<tr>
<td>ACEi</td>
<td>angiotensin-converting enzyme inhibitor(s)</td>
</tr>
<tr>
<td>ACR</td>
<td>albumin-creatinine ratio</td>
</tr>
<tr>
<td>ADPKD</td>
<td>autosomal dominant polycystic kidney disease</td>
</tr>
<tr>
<td>ADPLD</td>
<td>autosomal dominant polycystic liver disease</td>
</tr>
<tr>
<td>ADTKD</td>
<td>autosomal dominant tubulointerstitial kidney disease</td>
</tr>
<tr>
<td>AKI</td>
<td>acute kidney injury</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine transaminase</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin II-receptor blocker</td>
</tr>
<tr>
<td>ARPKD</td>
<td>autosomal recessive polycystic kidney disease</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
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<tr>
<td>AVP</td>
<td>arginine vasopressin</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CRISP</td>
<td>Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomography angiograph</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DSA</td>
<td>digital subtracted angiography</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>EO</td>
<td>early onset</td>
</tr>
<tr>
<td>ERKNET</td>
<td>European Rare Kidney Disease Reference Network</td>
</tr>
<tr>
<td>ERT</td>
<td>Evidence Review Team</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>glucagon-like peptide-1 receptor agonist</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<tr>
<td>HALT-PKD</td>
<td>HALT Progression of PKD</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>htLCV</td>
<td>height-adjusted liver cyst volume</td>
</tr>
<tr>
<td>htLV</td>
<td>height-adjusted liver volume</td>
</tr>
<tr>
<td>htTKV</td>
<td>height-adjusted total kidney volume</td>
</tr>
<tr>
<td>ICA</td>
<td>intracranial aneurysms</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
</tr>
<tr>
<td>IUD</td>
<td>intrauterine device</td>
</tr>
<tr>
<td>i.v.</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVF</td>
<td>in vitro fertilization</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease: Improving Global Outcomes</td>
</tr>
<tr>
<td>KRT</td>
<td>kidney replacement therapy</td>
</tr>
<tr>
<td>LAR</td>
<td>long-acting release</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function test</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
</tbody>
</table>
NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in October 2022. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Health-care professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually, and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members’ Disclosure section and is kept on file at KDIGO.

Note: This draft version of the KDIGO Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD is not final. Please do not quote or reproduce any part of this document.
WORK GROUP MEMBERSHIP

Work Group Co-Chairs

Olivier Devuyst, MD, PhD
University of Zurich, Zurich, Switzerland
UCLouvain Medical School, Brussels, Belgium

Vicente E. Torres, MD, PhD
Mayo Clinic
Rochester, MN, USA

Work Group

Curie Ahn, MD, PhD
Seoul National University
Seoul, South Korea

Michele Liew
Patient representative
Hong Kong, China

Thijs R.M. Barten, MD, PhD
Radboud University Medical Center
Nijmegen, The Netherlands

Andrew J. Mallett, MBBS, MMed, PhD
Townsville University Hospital
Townsville, QLD, Australia

Godela Brosnahan, MD
University of Colorado
Aurora, CO, USA

Changlin Mei, MD
Changzheng Hospital
Shanghai, China

Melissa A. Cadnapaphornchai, MD
Rocky Mountain Hospital for Children at Presbyterian St. Luke’s Medical Center
Denver, CO, USA

Djalila Mekahli, MD, PhD
University Hospital Leuven
Leuven, Belgium

Arlene B. Chapman, MD
University of Chicago
Chicago, IL, USA

Dwight Odland
PKD Foundation
Los Angeles, CA, USA

Emilie Cornec-Le Gall, MD, PhD
Centre Hospitalier Universitaire de Brest
Brest, France

Albert C.M. Ong, DM, MA, FRCP
University of Sheffield
Sheffield, United Kingdom

Joost P.H. Drenth, MD, PhD
Radboud University Medical Center
Nijmegen, The Netherlands

Luiz F. Onuchic, MD, PhD
Universidade de São Paulo
São Paulo, Brazil

Ron T. Gansevoort, MD, PhD
University of Groningen
Groningen, The Netherlands

York P-C Pei, MSc, MD, FRCPC
University of Toronto
Toronto, ON, Canada

Peter C. Harris, PhD
Mayo Clinic
Rochester, MN, USA

Ronald D. Perrone, MD
Tufts University School of Medicine
Boston, MA, USA
Methods Chair
Reem A. Mustafa, MD, PhD, MPH

Evidence Review Team
Center for Evidence Synthesis in Health, Brown University School of Public Health Providence, RI, USA
Ethan M. Balk, MD, MPH, Project Director, Evidence Review Team Director
Craig E. Gordon, MD, MS, Assistant Project Director, Evidence Review Team Associate Director
Gaelen P. Adam, MLIS, MPH, Senior Research Associate, Information Specialist
Ian J. Saldanha, MBBS, MPH, PhD, Researcher
Michael Zahradnik, BS, Research Associate
Wangnan Cao, PhD, Research Associate
Lucille Xiang, MPH, Research Assistant
INTRODUCTION FROM THE GUIDELINE CO-CHAIRS

Autosomal dominant polycystic kidney disease (ADPKD) is a major genetic disorder affecting up to 12 million people worldwide and the 4th most common global cause for kidney replacement therapy (KRT). A Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on ADPKD held in Edinburgh (January 16–19, 2014) brought together a panel of multidisciplinary experts and engaged patients from 20 countries. The panel assessed the state of knowledge and disparities among different countries and centers related to the evaluation, management, and treatment of ADPKD; identified outstanding knowledge gaps and controversial issues; and ascertained the timeline for the development of a clinical practice guideline made up of recommendations and practice points for ADPKD.

Since the Controversies Conference on ADPKD in 2014, genetic testing has become more accurate, readily available, affordable, and utilized. At least 7 genes in addition to PKD1 and PKD2, have been associated with ADPKD, increasing the complexity and clinical implications of its genetic landscape. Advanced imaging modalities of the kidneys and liver have defined typical and atypical entities and are now as critical to clinical decision-making in ADPKD as kidney biopsy is for glomerular diseases. Long-term observations of the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP), including the impact of imaging, genetic, and other biomarkers on estimated glomerular filtration rate (eGFR) trajectories, have been published. Prognostication tools for ADPKD have been validated and are utilized for clinical decision-making and planning of clinical trials. New clinical features, including early manifestations in children, have been described. Results of randomized clinical trials of tolvaptan in early and late ADPKD, long-acting somatostatin analogues in ADPKD and/or autosomal dominant polycystic liver disease (ADPLD), different blood pressure (BP) targets and levels of renin-angiotensin blockade in people with ADPKD, and other potential treatments for ADPKD and/or ADPLD have been published. Secondary analyses of these trials have explored effects of metabolic, dietary, and lifestyle factors. Tolvaptan has been approved for the treatment of rapidly progressive ADPKD in Japan, the European Union, Switzerland, the United States, Canada, Republic of Korea, Australia, and New Zealand. Long-acting somatostatin analogues are increasingly used to treat severe polycystic liver disease (PLD) when other options are not available. These advances have increased the awareness for the disease, triggering the publication of clinical practice guidelines in various countries. With the rapid increase in knowledge and expansion of information, the publication of a global KDIGO guideline for ADPKD has now become appropriate and most timely.

KDIGO guidelines for the Evaluation and Management of Chronic Kidney Disease (CKD), for the Management of Blood Pressure in CKD, and for the Care of Kidney Transplant Recipients have been published. The KDIGO Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD focuses on aspects of management that differ from those
for other CKD, while referring to appropriate, published guidelines when they are the same. The guidelines concentrate on clinical management questions that are addressed with high-quality scientific evidence in a systematic review generated by the Evidence Review Team (ERT). These include questions addressed by randomized trials that evaluated clinically relevant outcomes. Practice points are also made when a clinical question was not deemed a high priority for systematic review, to help readers implement the guidance from graded recommendation, or for issuing “good practice statements” when the alternative is considered to be absurd. The guidelines are sensitive to and have considered disparities in different parts of the world regarding availability of resources, as well as possible cultural differences.

The framework for the KDIGO Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD has been adapted from the breakout topics of the KDIGO Controversies Conference:

- Chapter 1 provides diagnostic criteria based on phenotypic and genetic characteristics; and prognostication based on imaging, genetic, and clinical biomarkers and proposes an expanded nomenclature of ADPKD and ADPLD that includes genetic information, when available.
- Chapter 2 provides recommendations for treating high BP, based on the HALT-PKD trials and practice points for evaluating and managing chronic kidney pain, nephrolithiasis, hematuria, urinary tract infection, renal cell carcinoma, and gout in people with ADPKD.
- Chapter 3 discusses recommendations and practice points for CKD and KRT, focusing on issues that are specific to ADPKD.
- Chapter 4 is dedicated to disease-modifying therapies, such as tolvaptan, and possibly modifying therapies such as long-acting somatostatin analogues, dietary, and other pharmacologic interventions.
- Chapter 5 presents statements on the evaluation and individualized management of PLD and on evaluation and treatment of liver cyst infection.
- Chapter 6 offers recommendations and practice points on whether, when, and how to screen people for the presence of unruptured intracranial aneurysms and measures to reduce the risk of development and rupture.
- Chapter 7 includes practice points addressing lifestyle and psychosocial issues in ADPKD and the importance of a multidisciplinary care team.
- Chapter 8 discusses practice points that relate to pregnancy, including maternal and fetal outcomes and reproductive issues.
- Chapter 9 discusses pediatric issues with ADPKD, including whether, when, and how to diagnose ADPKD in children at risk; high BP screening; initiation of antihypertensive treatment; BP target and monitoring; optimal models of care; and pediatric to adult transition.
• Chapter 10 stresses the importance of life-long, comprehensive, patient-centered management in multidisciplinary ADPKD clinics, supported by national health systems, insurers, and private payers, and enhanced by focused patient organizations, national kidney federations, scientific societies, and working groups.

As Co-Chairs, we want to recognize the outstanding effort of the Work Group, the ERT, the reviewers and consulted specialists, and the KDIGO staff. The Work Group was diverse, multinational, experienced, and dedicated to ADPKD. Notably, the Work Group included 3 members who have ADPKD and contributed greatly to keep the guideline relevant and patient-centered. We are indebted to all and hope that these guidelines will help improve the care of people with ADPKD.

Olivier Devuyst, MD, PhD
Vicente Torres, MD, PhD
ADPKD Guideline Co-Chairs
SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

CHAPTER 1. NOMENCLATURE, DIAGNOSIS, PROGNOSIS, AND PREVALENCE

1.1. Definition and nomenclature
Practice Point 1.1.1: In genetically defined people with autosomal dominant polycystic kidney disease (ADPKD), a common nomenclature should include the disease name followed by the gene name.

Practice Point 1.1.2: People who have an ADPKD or autosomal dominant polycystic liver disease (ADPLD) spectrum phenotype but have not been genetically screened will continue to be termed ADPKD or ADPLD.

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

Practice Point 1.1.4: For people who are genetically screened, ADPKD will be employed as the name of the disease resulting from mutation to the major ADPKD genes, PKD1 or PKD2, and the minor ADPKD loci.

Practice Point 1.1.5: For people who are genetically screened, ADPLD will be employed as the disease name for the major ADPLD genes, PRKCSH or SEC63, and the minor ADPLD loci.

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 patient need to be educated about the significance of the ADPKD and ADPLD nomenclature.

1.2. Prevalence
1.2.1. Prevalence of ADPKD in kidney failure populations.
[No recommendations and practice points]
1.3. Diagnosis

**Figure 3. Diagnosis algorithm in at risk adults (positive family history) for autosomal dominant polycystic kidney disease (ADPKD).** *Ultrasound and †MRI diagnostic criteria as described. MRI criteria relevant in typical ADPKD only.²⁴, ²⁵ †Genetic testing of genes shown in Figures 1 & 2. Reasons for genetic testing are listed in Table 2. Solid lines indicate tests suggested and dashed lines those to consider. Blue lines show possible outcomes of testing. ACMG, American College of Medical Genetics and Genomics guidelines;⁴⁵ CT, computed tomography; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; US, ultrasound*

**Practice Point 1.3.1:** A multidisciplinary team should be involved when discussing issues related to diagnosing ADPKD in individual people and families.

**Practice Point 1.3.2:** Appropriate counseling about the possible benefits and harms before scheduling 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: When making an initial diagnosis of ADPKD in an adult at risk, we recommend first using abdominal imaging by ultrasound. Follow-up magnetic resonance imaging (MRI) or computed tomography (CT) imaging may clarify the diagnosis and can provide prognostic information through MIC classification (1B).

Practice Point 1.3.3: 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 (Figure 5 and Figure 6).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of cysts</th>
<th>PKD1 Predictive value of a negative test (%)</th>
<th>Sn (%)</th>
<th>PKD2 Predictive value of a negative test (%)</th>
<th>Sn (%)</th>
<th>Unknown gene type Predictive value of a negative test (%)</th>
<th>Sn (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–29</td>
<td>≥3 total</td>
<td>100</td>
<td>94</td>
<td>100</td>
<td>70</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>30–39</td>
<td>≥3 total</td>
<td>100</td>
<td>97</td>
<td>100</td>
<td>95</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>40–59</td>
<td>≥2 in each kidney</td>
<td>100</td>
<td>93</td>
<td>100</td>
<td>89</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>60+</td>
<td>≥4 in each kidney</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Figure 5. Ultrasound criteria for autosomal dominant polycystic kidney disease (ADPKD) diagnosis in people with a positive family history.*²⁴ ND, not determined; PKD, polycystic kidney disease; Sn, sensitivity

Practice Point 1.3.4: For people with a positive family history of ADPKD aged 16–40, the number of cysts seen on MRI have been described to diagnose or exclude ADPKD (Figure 7).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Test criterion (number of cysts)</th>
<th>PKD1 Predictive value of a negative test (%)</th>
<th>Sp (%)</th>
<th>PKD2 Predictive value of a negative test (%)</th>
<th>Sp (%)</th>
<th>Unknown gene type Predictive value of a negative test (%)</th>
<th>Sp (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–29</td>
<td>≥1 total</td>
<td>99</td>
<td>98</td>
<td>84</td>
<td>97</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>30–39</td>
<td>≥1 total</td>
<td>100</td>
<td>96</td>
<td>97</td>
<td>94</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>40–59</td>
<td>≥2 total</td>
<td>100</td>
<td>98</td>
<td>100</td>
<td>98</td>
<td>100</td>
<td>98</td>
</tr>
</tbody>
</table>

*Figure 6. Ultrasound criteria for autosomal dominant polycystic kidney disease (ADPKD) exclusion in people with a positive family history.*²⁴ PKD, polycystic kidney disease; Sp, specificity
Practice Point 1.3.5: For people with no known family history of ADPKD, kidney imaging plays an important role in the diagnosis of people with detected cysts.

Practice Point 1.3.6: Genetic testing can be helpful to diagnose ADPKD and can provide prognostic information. However, genetic testing is not required to make an initial diagnosis of ADPKD in a person with a typical presentation (Figure 3).

Practice Point 1.3.7: Genetic testing is particularly informative for people with an equivocal diagnosis based on kidney imaging and in the setting of a negative or unknown family history (Table 2).

<table>
<thead>
<tr>
<th>Situation</th>
<th>Genetic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited number of cysts</td>
<td>Positive result can show a genetic origin (minor gene or hypomorphic allele)</td>
</tr>
<tr>
<td>Variable disease severity in a family</td>
<td>Mosaicism or biallelic/digenic disease can explain some extreme variability</td>
</tr>
<tr>
<td>Atypical imaging, including asymmetric or unilateral disease</td>
<td>Positive result can show a genetic origin (mosaicism or minor gene involvement)</td>
</tr>
<tr>
<td>Discordance between structural (MIC) and functional (GFR) ADPKD severity*</td>
<td>Genetic testing may reveal an atypical form of the disease or additional genetic or contributory factors. Non-genetic factors may also be important.</td>
</tr>
<tr>
<td>Negative family history</td>
<td>Positive result can show a genetic origin (de novo mutation can be proven)</td>
</tr>
<tr>
<td>VEO-ADPKD</td>
<td>Biallelic disease may be found (Chapter 9)</td>
</tr>
<tr>
<td>Related living transplant donor (&lt;30 years and/or a few cysts detected)</td>
<td>Genetic testing can exclude the familial variant and test for other genetic causes</td>
</tr>
<tr>
<td>Family planning and PGD</td>
<td>Obtaining a genetic diagnosis can aid family planning and enable PGD (Chapter 8)</td>
</tr>
<tr>
<td>All people</td>
<td>Genetics can confirm the diagnosis, identify the responsible gene and variant, and provide prognostic information</td>
</tr>
</tbody>
</table>

Table 2. Situations where genetic testing can clarify the diagnosis and aid prognosis. For more information about mosaicism, and biallelic and digenic inheritance, see Practice Point 1.3.9. *Discordance may be reduced GFR without significant kidney enlargement or an older individual with large kidneys but
normal GFR. ADPKD, autosomal dominant polycystic kidney disease; MIC, Mayo Imaging Class; PGD, preimplantation genetic diagnosis; VEO, very early onset (see definition in Chapter 9)

Practice Point 1.3.8: Genetic testing can be useful for selection of a living related donor for transplantation, especially if imaging results are equivocal.

Practice Point 1.3.9: Genetic testing can be helpful in families with marked phenotypic variability, including very early onset (VEO)-ADPKD or a suspected *de novo* mutational event.

Practice Point 1.3.10: Several inherited diseases can clinically mimic ADPKD or ADPLD with kidney and/or liver cysts as part of their phenotype (Figure 8).
**Figure 8. Other disorders that present with kidney cysts.** AD, autosomal dominant; AR, autosomal recessive; CHF, congestive heart failure; CKD, chronic kidney disease; CNS, central nervous system; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; RCC, renal cell carcinoma

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease</th>
<th>Inheritance</th>
<th>Overlapping with ADPKD</th>
<th>Distinguishing from ADPKD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental disorders</td>
<td></td>
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<tr>
<td><strong>HNF1B</strong></td>
<td>HNF1B-related kidney disease</td>
<td>AD</td>
<td>Cystic kidney disease</td>
<td>Congenital kidney and urinary tract anomalies, pancreatic disease, elevated liver enzymes, hypoglycemia</td>
<td>Sometimes presents as ADPKD spectrum alone</td>
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<tr>
<td><strong>JAG1, NOTCH2</strong></td>
<td>Aplagile syndrome</td>
<td>AD</td>
<td>Kidney cysts</td>
<td>Hepatic bile duct paucity, cholestasis, cardiac, skeletal, facial and eye abnormalities, and dysplastic kidneys.</td>
<td>A major feature can be infundibular, small cystic kidneys and abnormal kidney function.</td>
</tr>
<tr>
<td>Collagen disorders</td>
<td></td>
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<tr>
<td><strong>COL4A1</strong></td>
<td>Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)</td>
<td>AD</td>
<td>Kidney cysts</td>
<td>Hematuria, retinal arterial tortuositutes, muscular contractures, and brain small vessel disease</td>
<td>Presentation with mild cystic disease and few other phenotypes has been described.</td>
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<tr>
<td><strong>COL4A3, COL4A4, COL4G5</strong></td>
<td>Alport spectrum</td>
<td>AD and X-linked</td>
<td>Kidney cysts</td>
<td>Thinning of the glomerular basement membrane, microhematuria</td>
<td>Occasionally, kidney cysts are the major presentation.</td>
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<tr>
<td>Urinary stone diseases (USD)</td>
<td></td>
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<tr>
<td><strong>CYPIA1, SLC34A1, RHOA</strong></td>
<td>A variety of USD</td>
<td>AR (AD)</td>
<td>Kidney cysts</td>
<td>Predominant phenotype of kidney stones, nephrocystinosis, and/or other mineralization</td>
<td>Usually limited cyst involvement. Many apply to other USDs.</td>
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<tr>
<td>ADPKD</td>
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<tr>
<td><strong>MUC1, MEN1, SEC63, UAforg</strong></td>
<td>Autosomal dominant tubulointerstitial kidney disease (ADTID)</td>
<td>AD</td>
<td>Kidney cysts</td>
<td>Reduced kidney function without increased kidney size due to fibrotic kidneys. Cysts, when present, occur late in the disease. No liver cysts</td>
<td>Hyperuricemia (low Fiuente) and gout are prominent in ADPKD-UMOD and anaemia and gout in ADPKD-HEF.</td>
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<tr>
<td>Reccessive PKD</td>
<td></td>
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<tr>
<td><strong>PHEK/PKD, LZTPI, CYST</strong></td>
<td>Autosomal recessive polycystic liver disease (ARPKD)</td>
<td>AR</td>
<td>Bilateral kidney cystic disease</td>
<td>Typical or severe/intermediate presentation of extreme kidney enlargement, but later childhood/adult milder PKD possible. Congenital hepatic fibrosis rather than PLD</td>
<td>Later onset kidney disease can mimic ADPKD, but kidney cysts usually do not increase in length over time and CHF is usually present.</td>
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<tr>
<td><strong>PHM2</strong></td>
<td>Hypereuricemic hyperpyrexia and polycystic kidney disease (PHPD)</td>
<td>AR</td>
<td>Kidney cysts</td>
<td>The kidney disease is ARPKD-like, but hypereuricemic hyperpyrexia is also found. Liver cysts are only rarely seen</td>
<td>Biallelic disease where at least one allele is the promoter variant (c.−167G&gt;T). Typical biallelic PHM2 disease causes the congenital disorder of glycosylation type 1a (CDG1A).</td>
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<tr>
<td>Tumorous disorders</td>
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<tr>
<td><strong>FLCN</strong></td>
<td>Birt-Hogg-Dubé syndrome</td>
<td>AD</td>
<td>Kidney cysts</td>
<td>Hair follicle hamartomas, kidney tumors, spontaneous pneumothorax, lung cysts</td>
<td>FLCN pathogenic variant described in person with FS: ADPKD and lung cysts.</td>
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<td><strong>TSC1, TSC2</strong></td>
<td>Tubersclerosis complex (TSC)</td>
<td>AD</td>
<td>Kidney cysts</td>
<td>Multisystem disorder with hamartomas in brain, skin, heart, kidneys (angiomylipomas), and/or lung; CNS manifestations: epilepsy, learning difficulties, behavioral problems</td>
<td>Kidney cysts can be a major presentation with limited additional phenotypes.</td>
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<tr>
<td>PKD/PKD</td>
<td>PKD/PKD-Contiguous gene syndrome (CGS)</td>
<td>AD</td>
<td>Severe, infantile PKD</td>
<td>Hamartoma and CNS manifestations of TSC</td>
<td>Early onset and severe PKD leading to early KF. Mosaicism is common, that may be associated with less severe PKD.</td>
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<tr>
<td><strong>VHL</strong></td>
<td>Von-Hippel-Lindau syndrome</td>
<td>AD</td>
<td>Kidney and pancreatic cysts</td>
<td>Familial cancer syndrome with malignant and benign neoplasms in retina, cerebellum, spinal hemangioblastoma, renal cell carcinoma, pheochromocytoma, and pancreatic tumors</td>
<td>Renal cell carcinoma develop from the kidney cysts.</td>
</tr>
<tr>
<td>Ciliopathies</td>
<td></td>
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<tr>
<td><strong>OTOF</strong></td>
<td>Oral-facial-digital syndrome 1</td>
<td>X-linked</td>
<td>Kidney cysts in females</td>
<td>Malformations of the face, oral cavity, including cleft lip/palate, and digits; and PKD with abnormal kidney function. Usually, lethal in males.</td>
<td>The PKD can mimic ADPKD, and the facial and digital phenotypes can be minimal.</td>
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<tr>
<td><strong>NPHP and other NPHP genes</strong></td>
<td>Neophosphatosis (NPHP)</td>
<td>AR</td>
<td>Cortico- medullary cysts</td>
<td>Childhood presentation with echogenicity, loss of cortico-medullary differentiation, small atrophic kidneys, and CKD</td>
<td>NPHP1, and other forms of NPHP, can first present in adulthood.</td>
</tr>
<tr>
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</tr>
<tr>
<td>Marvy genes</td>
<td>Spondylocalciolopathies such as Joubert, Bardet-Biedl, and Meckel syndrome, and short rib thoracic dysplasia</td>
<td>AR</td>
<td>Kidney cysts</td>
<td>Often infantile or childhood disorders. A wide range of autosomal developmental phenotypes are seen depending on the disorder, including CNS, digital, ocular, skeletal, hypothalamic, and hepatic disease</td>
<td>More than 100 genes associated with spondylocalciolopathies including kidney cysts have been described.</td>
</tr>
<tr>
<td>Acquired disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
<td>Simple cysts</td>
<td>Small number, below the cyst number/age range to define ADPKD</td>
<td>The number of simple cysts increases with age.</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td></td>
<td>Acquired cystic disease (ACD)</td>
<td>Acquired Kidney cysts</td>
<td>Usually only seen with severe CKD or after KF. Kidneys are not enlarged.</td>
</tr>
</tbody>
</table>
Practice Point 1.3.11: A targeted next generation sequencing (tNGS) panel or other clinically accredited genetic or genomic test should be employed when performing genetic testing in people with ADPKD.

Practice Point 1.3.12: Clinical genetic testing results should be reported according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Practice Point 1.3.13: Genetic testing is not always definitive in a person with ADPKD caused by mutations in PKD1 or PKD2 because screening methods do not detect all pathogenic variants and some variants are not classed as pathogenic using ACMG guidelines.

Practice Point 1.3.14: In a person with ADPKD and with a typical presentation, negative or uncertain genetic results do not exclude an inherited form of ADPKD.

Practice Point 1.3.15: In a person with ADPKD and atypical imaging or another unusual presentation, negative or uncertain genetic results do not exclude an inherited form of PKD.

Practice Point 1.3.16: In a family with a known gene variant, screening for the specific variant (Sanger sequencing) is usually sufficient to diagnose or exclude ADPKD or to determine affected status.

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 PKD1, the type of PKD1 mutation influences the severity of kidney disease.

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

Practice Point 1.4.1.4: Male sex is a prognostic factor of more severe disease in people with ADPKD with males generally having larger kidneys for age than females and progressing to kidney failure at approximately 5 years earlier than females.

Practice Point 1.4.1.5: Overweight and obesity are risk factors for faster progression of ADPKD.
Practice Point 1.4.1.6: Higher salt intake 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.

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

Practice Point 1.4.2.5: Ultrasound-determined TKV and kidney length measurements also have prognostic value.

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

Practice Point 1.4.2.3: When using the MIC for prognostics, exclude people with atypical imaging patterns (Class 2A and 2B) as htTKV does not predict kidney outcomes in these people.

Practice Point 1.4.2.4: When using the MIC to predict future kidney function, it is important to exclude people who have pathogenic variants in genes other than PKD1 or PKD2 as the predictions are likely unreliable in these people.

Practice Point 1.4.2.5: Ultrasound-determined TKV and kidney length measurements are less precise than measurements using MRI segmentation, but also have prognostic value.

Practice Point 1.4.2.6: Advanced MRI-based biomarkers may provide additional predictive value.

Practice Point 1.4.2.7: Assessment of kidney function as eGFR in relation to age and/or longitudinal eGFR slope data can aid the identification of people with ADPKD and rapidly progressive disease.

Practice Point 1.4.2.8: The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score can aid the identification of people with rapidly progressive disease over 35 years of age.

Practice Point 1.4.2.9: Urine and serum measured biomarkers are potentially useful to assess prognosis and monitor treatments in ADPKD.
2.1. Hypertension
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 (Figure 15).

**Figure 15. Blood pressure management in autosomal dominant polycystic kidney disease (ADPKD).**
ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; HBPM, home blood pressure monitoring; LVH, left ventricular hypertrophy; RAS, renin-angiotensin system.

The Work Group agrees that the following statements from the *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD* apply to people with ADPKD.157

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Non-pharmacologic interventions</th>
<th>Medical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HBPM is preferred to office only measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Consider ABPM in children, and in adults with difficult BP control, or LVH, proteinuria, or declining kidney function but normal office BP readings</td>
<td></td>
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<tr>
<td>- Consider work up for secondary high BP when &gt;3 BP medications are needed in the setting of medication and dietary compliance</td>
<td></td>
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<tr>
<td>- Reduce dietary sodium including minimizing processed foods</td>
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<td></td>
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<tr>
<td>- Optimize body weight with a healthy diet and regular exercise</td>
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<td></td>
</tr>
<tr>
<td>- Optimize pain management, including sympathetic renal nerve inhibition, if appropriate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Inhibition of RAS provides the cornerstone of BP management and includes the use of an ACEi or ARB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Optimize BP control with addition of diuretic therapy to RAS blockade, if needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 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).

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

**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 (ID).
Recommendation 2.1.4: For people with ADPKD ≥50 years of age and/or with more advanced CKD (CKD G3-G5), we suggest a target mean systolic blood pressure (SBP) <120 mm Hg, if tolerated, using standardized office blood pressure BP measurement (2B).

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).

We agree with the following statement from the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD and feel this recommendation should apply to people with ADPKD.157

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).

Practice Point 2.1.4: Resistant high BP requiring ≥3 drugs should be investigated for causes of hypertension other than ADPKD.

Practice Point 2.1.5: Echocardiogram and urinalysis should be performed to assess hypertensive end-organ damage.

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 or liver pain in ADPKD is best managed by a multidisciplinary team as indicated, including nephrology, radiology, algology, psychology or psychiatry, physiotherapy, urology, and hepatology.

Practice Point 2.2.3: Shared decision-making between the physician and the patient or caregiver should guide the decision on pain management strategies in ADPKD.

Practice Point 2.2.4: Nonpharmacological, noninvasive interventions should generally be considered as the initial treatment of chronic kidney pain in ADPKD.
Practice Point 2.2.5: Stepwise pharmacological treatment for chronic kidney pain in people with ADPKD should be implemented when physical therapy does not adequately relieve pain.

Practice Point 2.2.6: The sequential approach and best choice of invasive intervention for chronic kidney pain in ADPKD depends on cyst characteristics and on the local expertise of the surgeon/interventional radiologist which may vary between centers and countries. 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 center.

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.

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.

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.

2.3. Nephrolithiasis

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

Practice Point 2.3.3: People with ADPKD and 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 available.

The Work Group agrees that the following statements from the Canadian Urological Association Guideline: Evaluation and medical management of kidney stones for the general population apply to people with ADPKD. While the Work Group agrees with the statements
below, this is not a formal endorsement of the Canadian Urological Association guideline. Please refer to local guidelines for your region or setting, where available.

**Recommendations from the Canadian Urological Association Guideline: Evaluation and medical management of kidney stones**

**Recommendation 2.3.1:** All stone formers should be counselled to achieve a daily urine output of 2.5 l (2B).

**Recommendation 2.3.2:** Stone disease highly correlates with obesity, diabetes, and metabolic syndrome; patients should be counselled that proper management of these conditions may reduce their future stone risk (2D).

**Recommendation 2.3.3:** When possible, specific dietary assessments and recommendations should be made with the involvement of a registered dietitian (3C).

**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.

**2.4. Gout**

The Work Group agrees that the following statements from the [2020 American College of Rheumatology Guideline for the Management of Gout](https://www.rheumatology.org/patient-guideline/gout) for the general population apply to people with ADPKD. While the Work Group agrees with the statements below, this is not a formal endorsement of the American College of Rheumatology guideline. Please refer to local guidelines for your region or setting, where available.
Practice Point 2.4.1: People with ADPKD should not be treated for asymptomatic hyperuricemia.  

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

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).
2.5. Hematuria
Practice Point 2.5.1: Clinicians should be aware of the causes and natural history of hematuria in ADPKD to provide proper guidance and, if appropriate, reassurance.

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

2.6. Urinary tract infections
The Work Group agrees that the following statements from the American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) for the general population apply to people with ADPKD. While the Work Group agrees with the statements below, this is not a formal endorsement of the AUA/CUA/SUFU guideline. Please refer to local guidelines for your region or setting, where available.

<table>
<thead>
<tr>
<th>Recommendations from the American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation 2.6.1: Clinicians should not treat asymptomatic bacteriuria (ASB) in patients (1B).</td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td>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).</td>
</tr>
</tbody>
</table>

Practice Point 2.6.1: Recurrent UTIs in people with ADPKD should be investigated for a possible underlying predisposition.
Practice Point 2.6.2: Before antibiotics are started for UTI, especially for upper UTI and/or suspected kidney cyst infection, a urine culture should be conducted.

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 (Figure 17).

Figure 17. Diagnostic algorithm for infected kidney cyst. CT, computed tomography; $^{18}$FDG PET-CT, positron emission tomography with $^{18}$F-2-deoxy-2-fluoro-glucose integrated with computed tomography; Ga67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga et al.

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 ADPKD, if possible.
2.7. Renal cell carcinoma

Practice Point 2.7.1: In the current state of knowledge, there is no clear association between ADPKD and an increased risk of renal cell carcinoma (RCC).

Practice Point 2.7.2: Clinicians should be aware of atypical presentation of RCC in ADPKD.
CHAPTER 3. CHRONIC KIDNEY DISEASE (CKD) MANAGEMENT AND PROGRESSION, KIDNEY FAILURE, AND KIDNEY REPLACEMENT THERAPY

3.1. CKD management and progression
Practice Point 3.1.1: In general, management of CKD in ADPKD is similar to that in 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 limit access to kidney transplantation.

Practice Point 3.1.3: Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI) should not routinely be used to manage anemia in people with ADPKD.

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

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.

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

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

Practice Point 3.2.6: 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 BMI.

Recommendation 3.2.1: We suggest that native kidney nephrectomy in people with ADPKD receiving a kidney transplant should be performed only for specific indications where the benefit outweighs the risk (Figure 22) (2C).

Practice Point 3.2.7: Shared decision-making with patients pretransplant and multidisciplinary case conferencing should contribute to the decision regarding performing and timing of nephrectomy.

Practice Point 3.2.8: People with ADPKD should be treated with the same immunosuppressive protocols as other transplant recipients.

<table>
<thead>
<tr>
<th>Potential Indications for Native Kidney Nephrectomy in People with ADPKD Receiving a Kidney Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent and/or severe kidney infection</td>
</tr>
<tr>
<td>Symptomatic nephrolithiasis</td>
</tr>
<tr>
<td>Recurrent and/or severe kidney cyst bleeding</td>
</tr>
<tr>
<td>Intractable pain</td>
</tr>
<tr>
<td>Suspicion of kidney cancer</td>
</tr>
<tr>
<td>Insufficient space for insertion of a kidney graft</td>
</tr>
<tr>
<td>Ventral hernia in the setting of massively enlarged kidneys</td>
</tr>
<tr>
<td>Severe symptoms related to massively enlarged kidneys*</td>
</tr>
</tbody>
</table>

Figure 22. Potential indications for native kidney nephrectomy in people with autosomal dominant polycystic kidney disease (ADPKD) receiving a kidney transplant. People with CKD should be asked for pain and volume related complaints in a structured manner, preferably using a questionnaire (e.g., the ADPKD-PDS, the ADPKD-IS and the GI symptom questionnaires).

Recommendation 3.2.2: We suggest unilateral rather than bilateral native kidney nephrectomy in people with ADPKD, when appropriate (2D).
Recommendation 3.2.3: We suggest that kidney transplant candidates with ADPKD who require native kidney nephrectomy undergo the procedure at the time of or after, but not before, transplantation, whenever possible (2C).

Practice Point 3.2.9: Nonsynchronous native kidney nephrectomy and shared decision-making may be considered given additional potential challenges associated with nephrectomy undertaken synchronously with kidney transplantation.

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

Practice Point 3.2.10: Evaluation for RCC in pretransplant people with ADPKD should be individualized and imaging of the kidneys (e.g., abdominal MRI) within 1 year prior to transplantation should be considered.

3.3. Kidney replacement therapy
Practice Point 3.3.1: Shared decision-making between physician and patient should be undertaken for choice of dialysis modality.

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 hemodialysis and supportive therapies, such as anticoagulation, should be the same as 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: We recommend initiating tolvaptan treatment in adults with ADPKD aged 18-55 years with an estimated glomerular filtration rate (eGFR) ≥25 ml/min/1.73 m² who have or are at risk for rapidly progressive disease (Figure 25) (1B).

| Initiation of tolvaptan should be offered to adult ADPKD patient with: |
|--------------------------|-----------------|
| • Age ≤55 years          |
| • eGFR ≥25 ml/min per 1.73 m² |

Risk of rapid disease progression* as indicated by:

• Historical rapid eGFR decline, with no other confounding cause than ADPKD (reliable eGFR decline ≥3 ml/min per 1.73 m² per year over ≥5 years†)

and/or

Predicted rapid progression by baseline htTKV indexed for age and:

• Mayo class 1D or 1E
• Mayo class 1C with additional evidence of rapid disease progression‡

Figure 25. The Kidney Disease: Improving Global Outcomes (KDIGO) algorithm to decide to whom to prescribe tolvaptan. *Rapid disease progression is defined as reaching or expected to reach kidney failure due to autosomal dominant polycystic kidney disease (ADPKD) before the age of ~60 years, the average age at which untreated people with ADPKD reach kidney failure. The age of ~60 years is based on multiple cohort studies (ERA-EDTA, mean age 58 years; Genkyst cohort 61.7 years; Mayo PKD Database 62 years; Korea national cohort 62 years; ANZDATA registry 60 years which has been stable since the 1990s. †In case of likely alternative explanations for estimated glomerular filtration rate (eGFR) loss (e.g., vascular disease, uncontrolled hypertension, diabetic nephropathy, proteinuria ≥1 g/d), initiation of tolvaptan should be reconsidered even in the presence of rapid eGFR decline. In these cases, additional information (including magnetic resonance imaging [MRI] or computed tomography [CT] imaging if not performed before; PROPKD score >6, a family history with onset of kidney replacement therapy (KRT) <60 years in ≥2 first-line family members) should be acquired to ensure ADPKD as the primary reason for eGFR loss. ‡Because some people with
Mayo Class 1C may not have rapid disease progression, we advise considering additional information, particularly in the people with age-adjusted height-adjusted total kidney volume (htTKV) close to Mayo Class 1B, to confirm the risk for rapid disease progression (e.g. evidence of eGFR decline or of a reduced age calibrated eGFR). Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score >6, family history with onset of KRT <60 years in ≥2 first-line family members, or novel biomarkers)

Practice Point 4.1.1.1: Shared and individualized decision-making should be undertaken when deciding to initiate tolvaptan in people >55 years old.

Practice Point 4.1.1.2: To determine eligibility for tolvaptan treatment, rapid disease progression is defined as a confirmed annual eGFR decline ≥3 ml/min per 1.73 m², based on ≥5 measurements over a period of ≥5 years. Evidence for rapid disease progression is also present if a person with ADPKD has CKD G3-G5 before age 45 years, enlarged kidneys, and no other explanation for reduced kidney function.

Practice Point 4.1.1.3: The Mayo Imaging classification, based on MRI, should be used as the primary imaging method for risk prediction and in consideration of tolvaptan in routine clinical care.

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

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.

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 (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 (Figure 28).

Practice Point 4.1.3.4: Tolvaptan should be discontinued prior pregnancy and to the commencement of KRT.
Figure 28. Commencement and titration approach to tolvaptan in ADPKD. *Examples of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (reduce clearance by >80%): antifungals (itraconazole, ketoconazole), antibiotics (clarithromycin), protease inhibitors (saquinavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir). Examples of moderate CYP3A inhibitors (reduce clearance by 50%–80%): antiarrhythmics (amiodarone), antifungals (fluconazole), antibiotics (erythromycin), calcium channel blockers (diltiazem, verapamil), protease inhibitors (amprenavir, fosamprenavir); complementary/dietary agents: grapefruit juice (240 ml coadministration)

4.1.4. Counseling people with ADPKD who are receiving tolvaptan
Practice Point 4.1.4.1: Physicians should be aware 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 written information about drug-drug interactions.

Practice Point 4.1.4.2: Education should be provided to people with ADPKD regarding the adverse effects of tolvaptan related to 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 aquaresic side effects to ensure long-term tolerability.

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

Practice Point 4.1.4.4: People with ADPKD should be advised to skip doses of their tolvaptan in situations associated with risk of dehydration, such as limited access to water (including hiking or traveling), diarrhea, or vomiting, and when activities in warm weather increase insensible water loss.

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.
Figure 29. Monitoring and management for potential hepatotoxicity in people with ADPKD on chronic treatment with tolvaptan. ALT, alanine transaminase; AST, aspartate aminotransferase; ULN, upper limit of normal.

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: Treatment with tolvaptan can be maintained until people with ADPKD approach the need of KRT initiation. Discontinuation may slightly increase eGFR.

Practice Point 4.1.6.4: People with ADPKD should be counselled regarding measures that can decrease polyuria during treatment with tolvaptan, including lowering dietary sodium and moderate reduction of dietary protein. Until further studies are available, concomitant medications should not be used to mitigate tolvaptan-induced aquarexis.
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 liters of urine 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 4.2.1.2: People with ADPKD should be provided specific advice and education on how much water to drink daily, how to achieve this, what fluids to drink, and how to determine if they are drinking sufficient quantities of water.

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 dilution 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.

4.3. Mammalian target of rapamycin 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).

4.6. Somatostatin analogues
Recommendation 4.6.1: We suggest that somatostatin analogues should be prescribed only 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(2B).
Practice Point 4.6.1: Somatostatin analogues should not be prescribed for the sole purpose of improving the rate of eGFR loss in people with ADPKD.

4.7. SGLT2 inhibitors
Practice Point 4.7.1: SGLT2 inhibitors should not be used to slow the rate of eGFR decline in people with ADPKD, until further research determines their efficacy and safety.

4.8. Complementary medicines
Practice Point 4.8.1: Complementary medicines or supplements should not replace standard medical treatments and people with ADPKD should share their intended or ongoing use of complementary medicines with their healthcare team.
CHAPTER 5. POLYCYSTIC LIVER DISEASE

5.1. Diagnosis and staging of PLD
Practice Point 5.1.1: The liver should be included when abdominal imaging is performed, preferably using CT scan or MRI, in people with ADPKD 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).

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 counselled about the benefits and potential harms of sex hormone therapy.

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.

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

5.2.3. Management
Practice Point 5.3.3.1: 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.

Recommendation 5.2.3.1: We suggest prescribing long-acting somatostatin analogues in people with ADPKD and markedly enlarged polycystic liver with severe volume related symptoms (2B).

Practice Point 5.2.3.3: When long-acting somatostatin analogues are prescribed, the effect on symptom burden and/or volume of polycystic liver and kidneys should be evaluated after 6 months. When beneficial effects of therapy are not observed, somatostatin analogues should be discontinued.

Practice Point 5.2.3.4: Ursodeoxycholic acid, mTOR inhibitors, and vasopressin-2 (V2) receptor antagonists should not be used to slow liver growth in people with PLD.

Practice Point 5.2.3.5: 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 5.2.3.6: People with PLD should be referred for combined kidney-liver transplantation when there is an indication for liver transplantation and the person has severely impaired kidney function (eGFR of <30 ml/min per 1.73 m²).

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 (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: Empiric 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.

5.3.2. Management

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

Practice Point 5.3.2.2: Empiric treatment of liver cyst infections should be initiated with a third-generation intravenous cephalosporin with or without a fluoroquinolone. After clinical stabilization, intravenous 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, and longer treatment periods may be required based on the response to therapy.

Practice Point 5.3.2.4: 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 risk factors listed below and kept in place until drainage stops. In the case of deep cysts where percutaneous drainage is not feasible, surgical drainage may be necessary.

Practice Point 5.3.2.5: It may be reasonable to perform percutaneous drainage of infected liver cysts <48 hours after initiation of antibiotics in the presence of the following:

- Isolation of pathogens that are unresponsive to antibiotic therapy from a cyst aspirate,
- Immunocompromised people,
- Large infected hepatic cysts (>8 cm),
- Hemodynamic instability and/or signs of sepsis.
CHAPTER 6. INTRACRANIAL ANEURYSMS (ICA) AND OTHER EXTRARENAL MANIFESTATIONS

6.1. Intracranial aneurysms (ICA)

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

<table>
<thead>
<tr>
<th>Prevalence of ICA (95% CI)</th>
<th>General population</th>
<th>General population plus family history of ICA or SAH</th>
<th>ADPKD population</th>
<th>ADPKD population plus family history of ICA or SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2% (1.9–5.2)</td>
<td>4% (2.6–5.8)</td>
<td>11% (9–14)</td>
<td>12.9% (10.4–15.4) (Figure 36)</td>
<td>18% (13–24)</td>
</tr>
<tr>
<td>0.079 (0.069–0.09)</td>
<td>3–7 higher risk</td>
<td>0.57 (0.19–1.14)</td>
<td>Likely higher (based on data from general population)</td>
<td></td>
</tr>
</tbody>
</table>


Practice Point 6.1.1. All people with ADPKD should be educated to recognize thunderclap headache which 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 at higher risk for ICA.
Practice Point 6.1.3: Because tobacco exposure is a strong modifiable factor for ICA development and rupture, clinicians 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 strong 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 in those at an increased risk for ICA (Chapter 2).

Practice Point 6.1.5. People should be informed of the implications of ICA screening as highlighted in Table 13.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>May allow adequate intervention if an ICA at risk of rupture is identified, allowing to prevent death or significant comorbidity.</td>
<td>Likely to identify ICA with very low risk of rupture ($\leq$5 mm/anterior circulation) and which do not require intervention but require long-term follow-up.</td>
</tr>
<tr>
<td>May reduce anxiety and provide reassurance when no ICA is detected</td>
<td>Does not exclude the risk of de novo ICA development and rupture after screening.</td>
</tr>
<tr>
<td></td>
<td>May lead to procedures with possible treatment failure or complications, including death or significant morbidity.</td>
</tr>
<tr>
<td></td>
<td>May cause anxiety when an ICA is identified.</td>
</tr>
<tr>
<td></td>
<td>May limit access to life insurance, loans, or driving licenses.</td>
</tr>
<tr>
<td></td>
<td>May limit work opportunities.</td>
</tr>
<tr>
<td></td>
<td>Cost associated with screening.</td>
</tr>
</tbody>
</table>

Table 13. Advantages and limitations of screening for unruptured intracranial aneurysms (ICA).

Recommendation 6.1.2. We recommend screening for ICA in people with a personal history of SAH or a positive family history of ICA, SAH, or unexplained sudden death if the person will be eligible for treatment and has reasonable life expectancy (ID).

Practice Point 6.1.6. Screening for unruptured ICA should also be discussed in people with de novo ADPKD, those with unknown familial history or small number of ADPKD-affected relatives, and in those with personal or familial history of extracerebral vascular phenotype.
Practice Point 6.1.7. Screening for unruptured ICA may also be considered 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: Time-of-flight (TOF) 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 an alternative.

Practice Point 6.1.10: If the screening is negative in people with high-risk of ICA, timing of rescreening should be individualized based on risk factors, age, and life expectancy.

Practice Point 6.1.11: 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.

6.2. Other vascular associations
Practice Point 6.2.1: There is no role for routine screening of vascular abnormalities of nonintracranial large arteries in people with ADPKD and no familial history of vascular aneurysms or dissections.

Practice Point 6.2.2: In case of familial history of aortic root or thoracic aortic aneurysms in people with ADPKD, screening of first-degree relatives should be performed.

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 include smoking cessation, statin therapy, and antihypertensive therapy including a beta-blocker and ACEi or ARB.

6.3. Cardiac associations
Practice Point 6.3.1: There is no role for routine baseline or surveillance echocardiography in people with ADPKD without signs or symptoms of cardiac dysfunction, heart murmur, or other cardiovascular manifestations.

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, especially in people with kidney and/or liver enlargement.

Practice Point 6.4.2: People with ADPKD 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 could be considered in people with ADPKD who elect PD as a mode of KRT, since increased abdominal pressure is a known risk factor for enlargement and complications of hernias.

6.5. Other extrarenal manifestations

[No recommendations and 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.

Practice Point 7.1.2: Physicians should work with accredited nutrition providers or registered dietitians to provide individualized nutrition counseling to people with ADPKD, particularly with CKD G4–G5.

Practice Point 7.1.3: People with ADPKD should maintain a healthy body weight.

Practice Point 7.1.4: Physicians should work with accredited nutrition providers or registered dietitians to help people with ADPKD who are overweight (BMI 25–29.9 kg/m²) or obese (BMI >30 kg/m²) to lose weight.

Practice Point 7.1.5: When calculating BMI, clinicians should take into account the weight of enlarged kidneys and liver.

Practice Point 7.1.6: People with ADPKD with poor oral intake due to organomegaly or advanced CKD (G4-G5) should be evaluated for malnutrition or sarcopenia.

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 at least 2 days per week.

Practice Point 7.2.2: People with large kidneys and/or liver should be advised of the possibility of direct injury 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 high-risk people with ADPKD such as those with CVD, frailty, bone disease, or risk of falling, and those on dialysis or after transplantation.

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 for women or ≤2 drinks per day for men.

7.3.3. Cannabis products
Practice Point 7.3.3.1: All people with ADPKD should be asked about their use of cannabis products and should be counselled about potential dangers of acute kidney injury (AKI) related to product contamination and synthetic versions.

7.3.4. Nephrotoxins
Practice Point 7.3.4.1: All people with ADPKD should be asked about their use of recreational drugs and anabolic steroids and should refrain from these drugs.

7.4 Psychosocial care
Practice Point 7.4.1: Healthcare providers should monitor a patient’s psychological health and social needs during clinic visits (Figure 42). Healthcare providers should screen and conduct periodic assessment of psychosocial issues in people with ADPKD (Figure 43).

Figure 42. Stressors associated with psychosocial problems in people with autosomal dominant polycystic kidney disease (ADPKD).
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 avoid unnecessary medical expenses.

Figure 43. Psychosocial manifestations, screening, and management. *See Appendix A
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, preconception counseling, and pregnancy management (Figure 45).

Practice Point 8.1.2: Since estrogen and possibly progesterone exposure may associate with an increased risk of PLD progression, women with ADPKD and liver cysts should be educated regarding their contraceptive choices (Chapter 5).

Practice Point 8.1.3: Contraception in adolescents should not be restricted.

Practice Point 8.1.4: When considering hormone therapy in women with ADPKD, liver imaging 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.

Practice Point 8.2.2: Preconception counseling should be provided by a multidisciplinary team in an ADPKD referral center when possible (Figure 46).
Figure 46. Multidisciplinary approach to preconception counseling. *Other specialties may be involved depending on the case (e.g., hepatologist, neurologist, etc.)

Practice Point 8.2.3: People with ADPKD at reproductive age should be offered appropriate counseling and all available reproductive options (Figure 47).

Figure 47. Reproductive options for people with ADPKD. ADPKD, autosomal dominant polycystic kidney disease

Practice Point 8.2.4: Tolvaptan, RASi (i.e., ACEi and ARBs), and any other teratogenic drug should be stopped prior to pregnancy and not restarted until the mother has completed breastfeeding.

Practice Point 8.2.5: Although men with ADPKD demonstrate increased prevalence of seminal tract cysts and sperm abnormalities, these do not appear to impact fertility, therefore, systematic screening is not indicated.
Practice Point 8.2.6: Before pregnancy, screening for ICA should be considered in women with family history of ICA.

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, and proteinuria should be monitored in women with ADPKD, similar to women with CKD.

Practice Point 8.3.3: Pregnant women with ADPKD should undergo monthly urinalyses performed. If a patient has a repeatedly positive urine culture, even when asymptomatic, they should be treated with appropriate antibiotics, as in the general population.

Practice Point 8.3.4: Women with ADPKD can safely undergo vaginal delivery, similar to the general population.

Practice Point 8.3.5: When a pregnant woman with ADPKD experiences an acute abdominal pain, imaging can be safely performed 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, most importantly, in those with preexisting hypertension or hypertension diagnosed during their pregnancy.

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

8.5. Preeclampsia
Practice Point 8.5.1: Women with ADPKD are at an increased risk of preeclampsia and preterm delivery and should be carefully monitored throughout their pregnancy and in the postpartum period.

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 (Figure 45).
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 outcome. 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 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 early (6 weeks) after delivery for a post-partum kidney review (Figure 49).

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 when tolvaptan will be prescribed.

![Test kidney function](image1)

![Reintroduction of medications depending on lactation state](image2)

![Return to pre-pregnancy target blood pressure](image3)

*Figure 49. Post-partum kidney review.*
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 are rarely perceived early in life. VEO-ADPKD and early onset (EO-ADPKD) forms of ADPKD are rare and distinct subentities of ADPKD (Table 15).

<table>
<thead>
<tr>
<th>Subentity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEO-ADPKD</td>
<td>Symptoms or clinical evidence of severe ADPKD under 18 months of age defined by:</td>
</tr>
<tr>
<td></td>
<td>• antenatal diagnosis of hyperechogenic enlarged kidneys (&gt;2 SD for gestational age) with oligohydramnios, OR</td>
</tr>
<tr>
<td></td>
<td>• enlarged cystic kidneys (&gt;2 SD for age, sex, height) between birth and 18 months of age with hypertension (BP ≥ 95th percentile for age, sex, and height) and/or decreased eGFR</td>
</tr>
<tr>
<td>EO-ADPKD</td>
<td>Symptoms or clinical evidence of severe ADPKD between 18 months and 15 years of age determined by:</td>
</tr>
<tr>
<td></td>
<td>• presence of enlarged cystic kidneys (&gt;2 SD for age, sex, and height) between 18 months and 15 years of age with hypertension (BP ≥ 95th percentile for age, sex, and height) and/or decreased eGFR</td>
</tr>
<tr>
<td>Child with ADPKD</td>
<td>A child with diagnosis of ADPKD not fulfilling VEO-ADPKD or EO-ADPKD criteria</td>
</tr>
<tr>
<td>Child at risk of ADPKD</td>
<td>A child in a family with ADPKD and at-risk</td>
</tr>
</tbody>
</table>

Table 15. Definitions of phenotypical entities in children with autosomal dominant polycystic kidney disease (ADPKD). BP, blood pressure; eGFR, estimated glomerular filtration rate; EO, early onset; SD, standard deviations; VEO, very early onset

Practice Point 9.1.2: Shared decision-making and a family-centered approach should be undertaken when discussing the benefits and harms related to diagnosis of at-risk children in families with ADPKD, including the parents/legal guardians and the mature child (Chapter 1; Figure 51).

Practice Point 9.1.3: Offer expert counseling about potential diagnostic options by a multidisciplinary team including a pediatric nephrologist and a geneticist with expertise in ADPKD to families with children at risk for ADPKD.

Practice Point 9.1.4: When diagnosis of ADPKD in children is desired, use ultrasound as the preferred imaging method.
Practice Point 9.1.5: Inform people and families that the presence of a single kidney cyst in a child with a positive familial history of ADPKD is highly suspicious for the diagnosis of ADPKD (Figure 50).

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 (Figure 50).

Practice Point 9.1.7: In children with kidney cysts and negative family history for ADPKD who seek diagnosis, perform ultrasound of the parents (or grandparents if parents <40 years) (Figure 50).

Practice Point 9.1.8: Consider a simple cyst as a differential diagnosis in children with an isolated cyst, negative family history, and negative ultrasound workup of the parents (or grandparents if parents <40 years).

Figure 50. Diagnosis of children with suspicion of autosomal dominant polycystic kidney disease (ADPKD). *Consider screening grandparents if parent screening is negative or parents <40 years of age. †e.g., very early onset ADPKD, significant kidney involvement. ADPKD, autosomal dominant polycystic kidney disease; VEO, very early onset

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.

Figure 51. Diagnosis of children at risk of autosomal dominant polycystic kidney disease (ADPKD).

*See Table 3 in Chapter 1.

9.2. BP control in children and adolescents with ADPKD

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

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

Practice Point 9.2.3: If ABPM is not available, routine in-office or HBPM are acceptable alternatives.
Practice Point 9.2.4: Evaluation of high BP in children and adolescents with or at risk for ADPKD should consider the possibility of primary or other secondary causes.

Practice Point 9.2.5: Echocardiography should be performed to exclude left ventricular hypertrophy (LVH) in children and adolescents with ADPKD and high BP.

Recommendation 9.2.1: We recommend targeting BP to \( \leq 50^{th} \) percentile for age, sex, and height or \( \leq 110/70 \) mm Hg in adolescents in the setting of ADPKD and high BP (ID).

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

Practice Point 9.2.6: 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 (Figure 52).
Figure 52. Follow-up of children with autosomal dominant polycystic kidney disease (ADPKD). ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; EO, early onset; NSAID, nonsteroidal anti-inflammatory drug; VEO, very early onset

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

Practice Point 9.3.3: Assessment of extrarenal manifestations is required only when there are concerning symptoms or to differentiate the findings from other cystic kidney diseases (Figure 52).

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: Manage abdominal pain in children with ADPKD the same as for children without ADPKD including an abdominal ultrasound. Use of nonsteroidal anti-inflammatory agents (NSAIDs) should be avoided or used sparingly for only a few days when absolutely needed.

Practice Point 9.3.7: Manage nephrolithiasis in children with ADPKD the same as for children without ADPKD. However, 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 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 (Figure 52 and 53).

Figure 53. Follow-up of children at risk for autosomal dominant polycystic kidney disease (ADPKD).
ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; NSAID, nonsteroidal anti-inflammatory drug.
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.

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.
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 (Figure 56).

Figure 56. A proposed autosomal dominant polycystic kidney disease (ADPKD) care pathway. eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PRO, patient-reported outcomes; TKV, total kidney volume; US, ultrasound. Adapted from Harris et al.,611; Mao et al.,718; Ong et al. 719

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.

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.
Practice Point 10.7: Healthcare systems should promote the participation of people with ADPKD to registries to 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 and families with ADPKD through provision of general information and peer support.
CHAPTER 1. NOMENCLATURE, DIAGNOSIS, PROGNOSIS, AND PREVALENCE

1.1. Definition and nomenclature

Autosomal dominant polycystic kidney disease (ADPKD) comprises a group of inherited disorders associated with kidney cysts and often extrarenal manifestations, caused by single pathogenic variants in one ADPKD gene (i.e., monoallelic), with autosomal dominant inheritance within families.\(^1\)\(^-\)\(^3\) Thus, children and siblings of people with ADPKD are normally at a 50% risk of also having ADPKD. Multigenerational families are common, but apparent *de novo* mutations are implicated in \(~20\%\) of families.\(^4\) The major genes causing ADPKD are *PKD1* and *PKD2*, together accounting for \(>90\%\) of affected families involved in research studies (Figure 1).\(^5\),\(^6\) However, several minor genes with an ADPKD spectrum phenotype have been described in the last decade that account for a small percentage of affected families.\(^7\)\(^-\)\(^11\) A major extrarenal manifestation of ADPKD is polycystic liver disease (PLD; see Chapter 5). A different monoallelic disease causing PLD, sometimes severe, but with no or few kidney cysts has been described, autosomal dominant polycystic liver disease (ADPLD), with the major genes being *PRKCSH* and *SEC63* (Figure 2).\(^12\)\(^-\)\(^14\) Single pathogenic variants to a few additional genes have been implicated in ADPLD,\(^15\) some of which can also result in an ADPKD phenotype (Figure 1). In addition, a group of simple and syndromic forms of polycystic kidney disease (PKD) can sometimes phenocopy or be misdiagnosed as ADPKD or ADPLD (see Section 1.3. Diagnosis; Figure 8).

**Practice Point 1.1.1:** In genetically defined people with autosomal dominant polycystic kidney disease (ADPKD), a common nomenclature should include the disease name followed by the gene name.

To help navigate the complexity of cystic kidney and liver diseases caused by a single pathogenic variant, we propose the naming scheme shown in Figures 1 and 2. The proposed format is a descriptor of the disease followed by the name of the gene, for example ADPKD-*PKD1*. This scheme of naming the disease and the gene is the one that has been successfully adopted by another type of dominantly-inherited kidney disease, autosomal dominant tubulointerstitial kidney disease (ADTKD), with ADTKD-*UMOD* and ADTKD-*MUC1* as descriptors of the major loci.\(^16\) This naming scheme is also being adopted more widely for monogenic disorders.\(^17\) This approach allows the disease name that nephrologists, other medical professionals, and affected people are familiar with to be maintained (such as ADPKD). Addition of the gene name allows characteristics of the disease associated with that specific gene to also be disseminated. We acknowledged that a shortened name for the disease, such as just PKD1 (for ADPKD-*PKD1*), may also appropriately be used.
<table>
<thead>
<tr>
<th>Gene</th>
<th>% screened families</th>
<th># of families</th>
<th>Disease designation</th>
<th>Kidney phenotype</th>
<th>Extrarenal phenotype</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unknown/not screened</strong></td>
<td></td>
<td></td>
<td>ADPKD</td>
<td>Bilateral PKD, kidney enlargement, age-related CKD, may result in KF</td>
<td>Liver cysts, including severe PLD, increased risk of ICA</td>
<td>A wide phenotypic range in terms of TKV and KF risk and timing</td>
</tr>
<tr>
<td><strong>PKD1</strong></td>
<td>~48%</td>
<td>&gt;3250</td>
<td>Truncating pathogenic variant: ADPKD-PKD1</td>
<td>Bilateral PKD, early kidney enlargement, CKD G3, ~40 y, KF in 50s</td>
<td>Liver cysts, including severe PLD, increased risk of ICA</td>
<td>Includes some disease variability including a more benign course, sometimes associated with mosaicism</td>
</tr>
<tr>
<td></td>
<td>~19%</td>
<td>&gt;1750</td>
<td>Nontruncating pathogenic variant: ADPKD-PKD1</td>
<td>Bilateral PKD, kidney enlargement, age-related CKD, may result in KF</td>
<td>Liver cysts, including severe PLD, increased risk of ICA</td>
<td>Phenotype ranges from severe as PKD1 truncating to mild PKD in old age, partly depending on the degree of residual protein function</td>
</tr>
<tr>
<td><strong>PKD2</strong></td>
<td>~15%</td>
<td>&gt;1000</td>
<td>ADPKD-PKD2</td>
<td>Bilateral PKD, milder and later kidney enlargement, CKD G3, ~55 y, KF in 70s</td>
<td>Liver cysts, including severe PLD, increased risk of ICA</td>
<td>Includes some disease variability including a more severe or more benign course</td>
</tr>
<tr>
<td><strong>ALG5</strong></td>
<td>~&lt;0.3%</td>
<td>&lt;10</td>
<td>ADPKD-ALG5</td>
<td>Mild to moderate cyst development with limited kidney enlargement and fibrosis CKD and some KF in older subjects</td>
<td>A few liver cysts in a minority of people</td>
<td></td>
</tr>
<tr>
<td><strong>ALG6</strong></td>
<td>~&lt;0.9%</td>
<td>&lt;10</td>
<td>ADPKD-ALG6</td>
<td>Generally mild with or without preserved kidney function</td>
<td>Liver cysts including severe PLD</td>
<td>Can present as ADPLD.¹</td>
</tr>
<tr>
<td><strong>ALG8</strong></td>
<td>~1%</td>
<td>&lt;40⁷</td>
<td>ADPKD-ALG8</td>
<td>Generally mild cystic kidney disease with preserved function into old age</td>
<td>Liver cysts, including severe PLD, ICA risk unclear</td>
<td>Can present as ADPLD. ALG8 is likely a low penetrant genotype.¹ ¹</td>
</tr>
<tr>
<td><strong>ALG9</strong></td>
<td>~&lt;0.3%</td>
<td>&lt;20</td>
<td>ADPKD-ALG9</td>
<td>Mild to moderate cystic disease with significant CKD in older people</td>
<td>Liver cysts are common</td>
<td></td>
</tr>
<tr>
<td><strong>DNAJB11</strong></td>
<td>~&lt;0.5%</td>
<td>&lt;30</td>
<td>ADPKD-DNAJB11</td>
<td>Bilateral small cysts, limited or no kidney enlargement, progressive fibrosis, limited CKD G3a ~55 y, but KF in 70s</td>
<td>Liver cysts, usually mild, ICA and vascular risk is possible</td>
<td>ADPKD-DNAJB11 has similarities to ADPKD, because of the small, fibrotic kidneys, but visible cysts are usually present</td>
</tr>
<tr>
<td><strong>GANAB</strong></td>
<td>~&lt;0.5%</td>
<td>&lt;20</td>
<td>ADPKD-GANAB</td>
<td>Mild cyst development, limited CKD, no KF</td>
<td>Liver cysts, including severe PLD, ICA risk unclear</td>
<td>Can present as ADPLD.</td>
</tr>
<tr>
<td><strong>IFT140</strong></td>
<td>~1%~2%</td>
<td>&lt;50</td>
<td>ADPKD-IFT140</td>
<td>Few, large bilateral cysts resulting in kidney enlargement, with kidney function usually preserved into old age</td>
<td>Liver cysts only rarely seen, with risk of ICA unclear</td>
<td></td>
</tr>
<tr>
<td><strong>NEK9</strong></td>
<td>~&lt;0.3%</td>
<td>&lt;20</td>
<td>ADPKD-NEK9</td>
<td>Bilateral PKD, kidney enlargement, KF in childhood, occasionally later in cases of specific alleles and mosaicism</td>
<td>Liver cysts rare</td>
<td>De novo occurrence was reported in 75% of the published cases.⁸</td>
</tr>
<tr>
<td><strong>PKHD1</strong></td>
<td>~1%</td>
<td>&lt;50⁷</td>
<td>ADPKD-PKHD1</td>
<td>Generally, very mild cystic kidney development with preserved function into old age</td>
<td>Liver cysts are common, and can be seen without kidney cysts</td>
<td>Bilalellic pathogenic variants are associated with ADPKD. Can present as ADPLD. Monocalellic PKHD1 is likely a low penetrant genotype.¹ ¹</td>
</tr>
<tr>
<td>Genetically unresolved by testing</td>
<td>~5%</td>
<td></td>
<td>ADPKD</td>
<td>Typically, mild cyst development with limited CKD and KF</td>
<td>Liver cysts</td>
<td>Most unresolved cases have relatively mild disease</td>
</tr>
</tbody>
</table>

¹ Data from reference [1].
² Data from reference [2].
³ Data from reference [3].
⁴ Data from reference [4].
⁵ Data from reference [5].
⁶ Data from reference [6].
⁷ Data from reference [7].
⁸ Data from reference [8].
Figure 1. Genes associated with the autosomal dominant polycystic kidney disease (ADPKD) spectrum and designations. The major ADPKD genes are bolded and shaded. *Estimate of number of published families. †Additional people with monoallelic loss of function variants have been identified but the kidney phenotype is unknown or nonpenetrant. AD, autosomal dominant; ADPLD, autosomal dominant polycystic liver disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; ICA, intracranial aneurysms; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; TKV, total kidney volume
<table>
<thead>
<tr>
<th>Gene</th>
<th>% screened families</th>
<th># of families *</th>
<th>Disease designation</th>
<th>Liver phenotype</th>
<th>Kidney phenotype</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not screened</td>
<td></td>
<td></td>
<td>ADPLD</td>
<td>Multiple liver cysts and often liver enlargement</td>
<td>None, or very few kidney cysts</td>
<td>Disease is highly variable from few liver cysts to massive PLD</td>
</tr>
<tr>
<td>PRKCSH</td>
<td>~20%</td>
<td>&gt;40</td>
<td>ADPLD-PRKCSH</td>
<td>Multiple liver cysts and often liver enlargement</td>
<td>None, or very few kidney cysts</td>
<td>Disease is highly variable from few liver cysts to massive PLD</td>
</tr>
<tr>
<td>SEC63</td>
<td>~15%</td>
<td>&gt;40</td>
<td>ADPLD-SEC63</td>
<td>Multiple liver cysts and often liver enlargement</td>
<td>None, or very few kidney cysts</td>
<td>Disease is highly variable from few liver cysts to massive PLD</td>
</tr>
<tr>
<td>ALG6</td>
<td>&lt;1%</td>
<td>&lt;10</td>
<td>ADPLD-ALG6</td>
<td>Liver cysts including severe PLD</td>
<td>Kidney cyst number variable from none to multiple</td>
<td>Can present as ADPKD.</td>
</tr>
<tr>
<td>ALG8</td>
<td>5−10%</td>
<td>&lt;20†</td>
<td>ADPLD-ALG8</td>
<td>Multiple liver cysts and often liver enlargement, but liver cysts may not be present</td>
<td>Kidney cyst number variable from none to multiple, including an ADPKD spectrum phenotype</td>
<td>Can present as ADPKD-ALG8. ALG8 is likely a lower penetrant phenotype</td>
</tr>
<tr>
<td>GANAB</td>
<td>1−5%</td>
<td>&lt;10</td>
<td>ADPKD-GANAB</td>
<td>Multiple liver cysts and often liver enlargement, but liver cysts may not be present</td>
<td>Kidney cyst number variable from none to multiple, including an ADPKD spectrum phenotype</td>
<td>Can present as ADPKD-GANAB</td>
</tr>
<tr>
<td>LRPS</td>
<td>&lt;1%</td>
<td>4</td>
<td>ADPKD-LRPS</td>
<td>Multiple liver cysts and often liver enlargement</td>
<td>None, or very few kidney cysts</td>
<td>Based on missense variants in 1 family and 3 people. Monoallelic LRPS variants are also associated with familial exudative vitreoretinopathy</td>
</tr>
<tr>
<td>PKHD1</td>
<td>~1%</td>
<td>&lt;25†</td>
<td>ADPLD-PKHD1</td>
<td>Generally, very mild cystic kidney development with preserved function into old age</td>
<td>Liver cysts are common and can be seen without kidney cysts. Not usually associated with severe PLD</td>
<td>Biallelic pathogenic variants are associated with ARPKD. Can present as ADPKD-PKHD1</td>
</tr>
<tr>
<td>SEC61B</td>
<td>&lt;1%</td>
<td>2</td>
<td>ADPLD-SEC61B</td>
<td>Numerous small cysts</td>
<td>Very few or none</td>
<td>Data based on 2 people</td>
</tr>
<tr>
<td>Genetically unresolved</td>
<td>~50%</td>
<td></td>
<td>ADPLD</td>
<td>Multiple liver cysts but tendency for milder PLD</td>
<td>None, or very few kidney cysts</td>
<td>Disease is highly variable from few liver cysts to massive PLD</td>
</tr>
</tbody>
</table>

*Figure 2. Genes associated with autosomal dominant polycystic liver disease (ADPLD) and designations.* The major genes are **bolded and shaded.** †Estimate of number of published families. ‡Additional people with monoallelic loss of function variants have been identified but the liver phenotype is unknown or
nonpenetrant; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; PLD, polycystic liver disease
Practice Point 1.1.2: People who have an ADPKD or autosomal dominant polycystic liver disease (ADPLD) spectrum phenotype but have not been genetically screened will continue to be termed ADPKD or ADPLD.

We understand that the diagnosis of ADPKD is most often made on clinical, imaging, and family history grounds, not by genetic testing, and we do not propose genetic testing for all people. Therefore, people who have the classical ADPKD spectrum phenotype of bilateral kidney cysts, often enlarged kidneys, the possibility of abnormal kidney function or kidney failure, and liver cysts but have not been genetically tested will continue to be termed ADPKD. Likewise, for people who have not been genetically tested but have moderate-to-severe PLD with only very few or no kidney cysts will continue to be termed ADPLD. When the individual person obtains a genetic diagnosis, the gene can be added to the disease name.

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

Genetic testing does not always provide a positive diagnosis. In the real-world clinical testing setting, the positive test rate may be ~75%, and is lower in people with atypical disease.\textsuperscript{18} Hence, in a significant proportion of people, no likely pathogenic variants are identified or only variants that are classed as variants of uncertain significance (VUS) are found. In these cases, if the phenotype is consistent with ADPKD or ADPLD, and no genetic or clinical data suggest a different form of cystic disease, the person will continue to have the clinical diagnosis of ADPKD or ADPLD.

Practice Point 1.1.4: For people who are genetically screened, ADPKD will be employed as the name of the disease resulting from mutation to the major ADPKD genes, PKD1 or PKD2, and the minor ADPKD loci.

The major genes for ADPKD are PKD1 and PKD2, and people with variants classed as “pathogenic” or “likely pathogenic” will be given the name ADPKD-PKD1 or ADPKD-PKD2, respectively (Figure 1). The minor genes that we also suggest including in the ADPKD group are ALG5, ALG6, ALG8, ALG9, DNAJB11, GANAB, IFT140, NEK8, and monoallelic PKHD1, with the designation, ADPKD-ALG5, etc., as listed in Figure 1.\textsuperscript{7-11, 19, 20} These genes have distinctive phenotypes but that overlap clinically with PKD1 and PKD2. This disease gene information can provide a general guide about the likely disease course and specific disease features to be aware of. For instance, people with typical ADPKD-IFT140 usually have increased total kidney volume (TKV) due to a few large cysts but a low risk of kidney failure (Figure 1).\textsuperscript{10} In contrast, ADPKD-DNAJB11 is typically associated with development of only a few small cysts and TKV is not increased, but there is high risk of kidney failure later in life due to kidney fibrosis.\textsuperscript{8, 21} Including the gene in the designation also identifies people with the minor genes for which treatment with the presently approved drug for ADPKD (tolvaptan) is not appropriate because similar people were not included in the clinical trials.\textsuperscript{22, 23} The use of cyst number criteria for diagnosing or excluding ADPKD\textsuperscript{24, 25} and employing the Mayo Imaging Class (MIC) to define patient outcomes\textsuperscript{26} should also be restricted to people with ADPKD-PKD1 and ADPKD-PKD2. Since ~5% of people with ADPKD
are genetically unresolved by testing, new genes will likely be identified that will need to be added to the current list of named ADPKD genes.

**Practice Point 1.1.5:** For people who are genetically screened, ADPLD will be employed as the disease name for the major ADPLD genes, PRKCSH or SEC63, and the minor ADPLD loci.

The major genes for ADPLD are PRKCSH\textsuperscript{12,13} and SEC63\textsuperscript{14,15} and people with variants classed as “pathogenic” or “likely pathogenic” will be given the name ADPLD-PRKCSH or ADPLD-SEC63, respectively. The minor ADPLD genes are: LRP5,\textsuperscript{27} GANAB, ALG6, ALG8, SEC61B, and monoallelic PKHD1,\textsuperscript{15} with the designation ADPLD-LRP5, etc. We have taken this approach because while there are limited data about the phenotypes associated with these minor loci, the available information indicates an overlap with the disease caused by pathogenic variants to the major genes. In addition, without a genetic diagnosis, these people would most likely have been given a clinical diagnosis of ADPLD. New ADPLD genes will likely be identified that will need to be added to the current list of named genes.

Although GANAB, ALG6, ALG8 and monoallelic PKHD1 often have an ADPLD phenotype, kidney cysts can be the predominant manifestation in some cases.\textsuperscript{7,18,28} Therefore, a nomenclature of, for instance ADPKD-GANAB or ADPLD-GANAB, should be used depending on whether the kidney or liver disease predominates. Due to varied presentations associated with pathogenic variants to these genes, both ADPKD-GANAB and ADPLD-GANAB can be defined in the same family. If no genetic data are available, the ADPKD or ADPLD designation should be used based on the disease presentation. GANAB, ALG6, and ALG8 can be associated with severe, clinically significant PLD (similar to PRKCSH and SEC63), whereas, liver cysts appear to be mainly small with minimal increases in liver volume for monoallelic PKHD1.\textsuperscript{7,15} ADPKD-PKD1 and ADPKD-PKD2 can present with severe PLD, and especially for PKD2, the kidney disease can be very mild, therefore, they may be designated as ADPLD-PKD2.

**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.

Information about the pathogenic variant, for instance, whether it is predicted to truncate the nascent protein product, can be phenotypically significant. Truncating pathogenic variants are defined as frameshifting deletions, duplications, or insertions; nonsense variants; canonical splicing variants; and large rearrangements (deletions, duplications, or insertions) involving at least one exon termed copy number variants (CNV). Nontruncating pathogenic variants are defined as small inframe deletions, duplications, or insertions, missense variants, and noncanonical splicing variants. People with ADPKD-PKD1 who have truncating variants have poorer kidney disease outcomes overall than those with nontruncating variants.\textsuperscript{29,30} Hence, while ADPKD-PKD1 is usually associated with the most severe kidney disease, some nontruncating alleles still generate a significant amount of functional protein (are partially penetrant or hypomorphic) and can, thus, be associated with less severe disease, including very mild PKD without risk of kidney failure.\textsuperscript{31,32} Therefore, whether the PKD1 variant is truncated or nontruncating should be indicated in diagnostic reports.
Nonetheless, a significant proportion of *PKD1* nontruncating alleles are likely full inactivating (no functional protein is generated from the pathogenic allele); *in silico* methods to try to differentiate alleles that are fully or partially penetrant are under development.\(^5\) Even some people with *PKD1* truncating variants can have milder kidney disease.\(^{33}\) The reason for this is not fully understood, but genetic modifiers, lifestyle, and other environmental factors are likely important. Therefore, because of the provisos indicated, whether *PKD1* pathogenic variants are truncating or nontruncating should not be added to the nomenclature at this time.

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

By adding the gene name to the ADPKD disease name, we believe that a better appreciation of the expected phenotype and outcomes will be provided than simply describing the disease as ADPKD alone. For example, for the many people with ADPKD-*PKD1*, especially if noted as a truncating change, are at high risk for future kidney failure, and treatment options may be suitable; while for the rarer ADPKD-*ALG8*, the chance of kidney failure is small, but more severe PLD may develop. Therefore, since the risk of kidney failure in people with ADPKD-*ALG8* is much less than for those with ADPKD-*PKD1* truncating, this should be reflected in their insurance risk. For this to happen, people with ADPKD, healthcare providers, and insurance companies will need to be educated about the risks of kidney failure and other complications associated with the different forms of ADPKD. Therefore, it will be important for the PKD community to actively educate these stakeholders, including partnering with PKD foundations and groups from around the world, to facilitate appreciation of this knowledge. Similar arguments can be made in terms of likely severity of disease and risk for family members for taking note of the causative ADPLD gene.

**1.2. Prevalence**

ADPKD is the most prevalent monogenic kidney disease associated with kidney failure, accounting for a significant proportion of the chronic kidney disease (CKD) and kidney failure populations.\(^{34}\) ADPKD affects all populations with no common pathogenic variant enriching the disease in a geographical area or racial/ethnic group. Some differences in prevalence may exist but there are limited data. Estimates of prevalence have varied by more than 5-fold, especially between population and genetic studies. This variability likely partially reflects incomplete identification of all people with ADPKD in population studies since the age-related phenotype can often go unrecognized for decades. The discrepancy is also related to what is defined as ADPKD especially at the mild end of the cystic kidney spectrum. Improved imaging indicates that multiple cysts in the kidney (above the Pei imaging diagnostic criteria\(^{24, 25}\)) are not such a rare occurrence- a significant proportion of which likely have a monogenic origin- broadening the genetic basis of ADPKD and weakly penetrant alleles at the major loci.

A prevalence of 1/1000 is an often quoted figure that is derived for the classic study by Dalgaard of the population in Copenhagen and published in the 1950s.\(^{35}\) The figures are in fact...
estimates of genetic prevalence of the disease at birth estimated from the theoretical risk of being ill from ADPKD during a lifetime of 80 years (of 8 per 10,000 people), rather than point prevalence data. In the past few years, several population studies have estimated the prevalence of ADPKD using various databases in European and the United States (U.S.; Supplementary Table S1). Estimates from these studies vary somewhat with a value of 3.96/10,000 in the European Union (EU) in 2012, between about 2–4 per 10,000 in various studies in the U.S., and a slightly higher level of 5.7/10,000 in the Seychelles, that seems to be concentrated in the European ancestral population, reflecting either a possible founder effect or an underserved Black population. A recent Olmsted County study (1980–2016) of the Rochester Epidemiology Database and radiological databases found a prevalence of 6.8/10,000 for “definite” and “likely” people with ADPKD. This increased to 12.4/10,000 when “possible” ADPKD people were included reflecting the frequency of those with mild cyst development. Analysis of an unselected health system-based cohort from Pennsylvania also found a high prevalence (13.5/10,000) selected by International Classification of Diseases (ICD) codes and clinically confirmed.

Lanktree et al. screened the sequenced gnomAD and BRAVO “normal” populations (total >200,000) for high-confidence pathogenic variants to PKD1 and PKD2 and determined a ADPKD prevalence of 9.3 cases per 10,000 sequenced. This estimate likely reflects undercounting of people with asymptomatic ADPKD in population studies, but also possibly that some proposed pathogenic variants do not result in clinically significant disease. Prevalence values for PKD1 and PKD2 were 6.8 and 2.6/10,000, respectively, resulting in a ratio of PKD1/PKD2 of 2.6. This is much lower than the >4 found in kidney clinic populations, probably reflecting the milder phenotype associated with PKD2 changes (people with PKD1 pathogenic changes may also be underrepresented in these “normal” populations). Following whole exome sequencing (WES) of the Geisinger population, a possible genetic cause was found in 180 of 235 people with ADPKD (76.6%), the majority being rare variants to PKD1 (n=127) or PKD2 (n=34), while 19 (8.1%) had variants in other genes associated with cystic kidney diseases. The high penetrance of PKD1 and PKD2 truncating variants was illustrated with 42/54 (77.8%) and 17/24 (70.8%) people with such a variant, respectively, ICD coded as ADPKD. This level was much lower for IFT140 (2.5%), GANAB (7.1%), and HNF1B (6.2%), indicating that ADPKD phenotypes are less penetrant for the minor ADPKD genes. Overall, prevalence differences likely reflect underdiagnosis of ADPKD in population studies, but it remains to be seen at what level high-confidence pathogenic variants to the various ADPKD genes result in clinically significant cystic outcomes.

1.2.1. Prevalence of ADPKD in kidney failure populations.

As well as being a common monogenic disease, ADPKD is an important cause of kidney failure. In the U.S. in 2020, the number of people with cystic kidneys starting kidney replacement therapy (KRT) was 3396, representing 2.60% of the KRT total. Not surprisingly given the inheritance pattern, more people with a cystic kidney were receiving nephrology care ≥12 months before kidney failure than any other kidney failure group (55.6%); however, 34.8% only started receiving nephrology care <1 year before kidney failure. In 2020, the number of people with a cystic kidney receiving KRT in the U.S. was 40,968 (i.e., 5.07% of the KRT total). This represents
115/million U.S. subjects. Of these, 63% had a kidney transplant, 29% were receiving hemodialysis (HD), and 8% peritoneal dialysis (PD).

In the European population collected in the European Renal Association (ERA) Registry in 2020, the prevalence of polycystic kidneys, ADPKD type was 6.5/million, representing 5% of the KRT population. In the <65 year age group, 9% of the KRT population had PKD, with 55% in the 45–64 year age range. In this PKD KRT population, 67% had a kidney transplant, 30% were receiving HD, and 3% PD.

1.3. Diagnosis

ADPKD accounts for 5%–10% of people with kidney failure worldwide, and therefore is a very significant health problem. Obtaining a firm diagnosis in ADPKD is a first step toward receiving appropriate care and, where possible, starting treatment. Traditionally, ADPKD has been diagnosed in at-risk family members of an affected subject (children, siblings, or occasionally a parent) by abdominal imaging (Figure 3). We continue to recommend imaging as the first entity to employ for ADPKD diagnostics. However, genetic testing has become widely available and employed in ADPKD families which can also be valuable. We also discuss how to obtain a firm diagnosis when kidney cysts are detected incidentally by imaging (Figure 4).
Figure 3. Diagnosis algorithm in at risk adults (positive family history) for autosomal dominant polycystic kidney disease (ADPKD). *Ultrasound and †MRI diagnostic criteria as described. MRI criteria relevant in typical ADPKD only. ‡Genetic testing of genes shown in Figures 1 & 2. Reasons for genetic testing are listed in Table 2. Solid lines indicate tests suggested and dashed lines those to consider. Blue lines show possible outcomes of testing. ACMG, American College of Medical Genetics and Genomics guidelines; 45 CT, computed tomography; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; US, ultrasound.
Figure 4. Diagnosis algorithm in adults with incidentally detected kidney and/or liver cysts (no known family history of ADPKD). *Genetic testing of genes shown in Tables 1 & 2. Reasons for genetic testing are listed in Table 1. Solid black lines indicate tests suggested and dashed lines those to consider. Blue lines show possible outcomes of testing. ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; US, ultrasound.

Practice Point 1.3.1: A multidisciplinary team should be involved when discussing issues related to diagnosing ADPKD in individual people and families.

Decisions about whether to undergo testing for ADPKD, abdominal imaging or genetic screening, should respect the wishes of people with ADPKD and their families. To ensure that informed decisions are made, healthcare providers should be able to explain the benefits and harms of performing the testing (Table 1) and articulate which are the appropriate testing methods according to the circumstances. This information about the testing should be offered before the testing is performed. Reasons for taking the tests vary depending on the circumstances of the individual person and their family. ADPKD can most often be diagnosed in people at risk by abdominal imaging, but genetic testing might be helpful in certain situations. The suggestions here are limited to diagnosing ADPKD in adults, with questions related to diagnosing ADPKD in children discussed in Chapter 9.
### Possible benefits of early screening

- **Resolve diagnosis odyssey.** The individual person and family may obtain a definite diagnosis.
- **Ability to manage and treat ADPKD.** Appropriate management and treatment of the affected person can be initiated.
- **Initiate screening for extrarenal manifestations.**
- **Enable enrollment in clinical trials.**
- **Reassurance of unaffected people.** Negative imaging and/or genetic testing results in at-risk family members will likely provide relief to the person and may influence family-planning decisions.
- **Appropriate family planning.** Knowledge about the genetic nature of ADPKD might aid decision-making concerning care of the person and family planning.
- **Appropriate selection of unaffected relatives as possible donors for kidney transplantation.** Negative imaging and/or genetic results can identify suitable living related donors.
- **Facilitate testing of family members.** A positive genetic test allows inexpensive screening of other interested at-risk family members, allowing appropriate management of those affected.
- **Implement lifestyle modifications.** Details in Chapter 7.

### Possible harms of early screening

- **Psychologic burden of having a life-altering diagnosis.** Obtaining a diagnosis of ADPKD may lead to a range of emotions (e.g., anxiety about the future, anger, guilt about transmission to offspring).
- **Possible difficulties with employment and insurability** Despite legislation in many countries, the diagnosis of a genetic disease can have certain insurance (e.g., life, health, disability) and workplace implications. However, it is important to consider that being at risk of ADPKD, without a firm diagnosis, may also have insurability implications.
- **High cost.** Some testing, including genetic testing and certain types of imaging, may not be fully covered by insurance or government funded health plans.
- **Imaging and/or genetic testing results may be inconclusive.** In >25% of cases genetic testing does not result in a certain diagnosis, and imaging can provide equivocal results. Both may lead to false reassurance and erroneous decision-making.
- **Specialist knowledge to interpret test results may not always be available.** Supply of professionals with genetics expertise for kidney diseases is limited.

<table>
<thead>
<tr>
<th>Possible benefits of early screening</th>
<th>Possible harms of early screening</th>
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</thead>
<tbody>
<tr>
<td>• Resolve diagnosis odyssey.</td>
<td>• Psychologic burden of having a life-altering diagnosis.</td>
</tr>
<tr>
<td>• Ability to manage and treat ADPKD.</td>
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<tr>
<td>• Facilitate testing of family members.</td>
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<tr>
<td>• Implement lifestyle modifications.</td>
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**Table 1. Benefits and harms of screening (by imaging and genetics) people at risk for autosomal dominant polycystic kidney disease (ADPKD).**

Table 1 outlines the potential benefits and harms of testing in people at risk for ADPKD. Although, there is strong evidence that testing to obtain a diagnosis of a genetic disease can be of value to the at-risk person and their family, there are also well-documented potential negative consequences that need to be considered when discussing options (Table 1). Attitudes to testing people at risk including when and how to provide the testing can vary between individual people, families, and cultures. These values and preferences, plus the availability of specific testing, need to be taken into consideration when counseling about testing options and likely outcomes and when explaining the results. The availability of specific tests, whether it is imaging or genetic testing, vary greatly between centers and in different parts of the world. Also, the costs of specific testing vary depending on the type of testing to be performed and the location. Of particular importance is the possible out of pocket costs of the testing that need to be carefully explained.
The involvement of a multidisciplinary team to perform diagnostics for ADPKD is advised. For genetic testing, this includes nephrologists and/or genetic counselors providing pretest counseling and medical geneticists experienced in ADPKD for interpreting genetic results.\textsuperscript{48} For radiological screening, a radiologist skilled in ADPKD should be involved. A team-based approach in nephrology can counsel the individual person and family, arrange sample collection, order the tests, interpret the results, return results to patients with appropriate counseling about the significance and make any recommendations for follow on studies.\textsuperscript{50-53} A counseling checklist can help the nephrology team outline the benefits and limitations of the different imaging and genetic testing methods. Patient information handouts can be helpful to explain the testing methods and risks and the significance of the genetic results that can also be utilized by their primary provider. The affected person should have contact information of the provider so that questions can be answered throughout the process.

**Practice Point 1.3.2: Appropriate counseling about the possible benefits and harms before scheduling 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.**

Counseling should be provided by a nephrologist with expertise in ADPKD, a genetic counsellor, or other medical professional to the person at risk for ADPKD both before kidney imaging or genetic analysis is performed and after the results are received to help interpret the results, understand their significance, and plan follow-up studies. This is important when the results are positive but also significant if the imaging or genetic results are equivocal and follow-up analyses are required. As indicated, a team-based approach to ordering testing is recommended. Primary care doctors should only initiate testing if they have the support network and experience to interpret the results and are prepared to refer those with positive findings to a nephrologist.

**Recommendation 1.3.1: When making an initial diagnosis of ADPKD in an adult at risk, we recommend first using abdominal imaging by ultrasound. Follow-up magnetic resonance imaging (MRI) or computed tomography (CT) imaging may clarify the diagnosis and can provide prognostic information through MIC classification (1B).**

This recommendation emphasizes the value of using abdominal imaging by ultrasound as the first method to screen a person at risk of ADPKD, even if follow-up studies may be of value to clarify and expand upon the initial ultrasound findings. There is moderate evidence to support this recommendation.

**Key information**

*Balance of benefits and harms*

Obtaining a diagnosis of ADPKD is key to the person being referred to a nephrologist with experience in ADPKD to oversee their care and ensure that clinical manifestations of the disease, such as early onset hypertension, are monitored and appropriately treated. We recommend using abdominal imaging performed by ultrasound to initially diagnose ADPKD in people at risk. (Figure
3). Ultrasound is noninvasive, generally available, and inexpensive. In situations where greater resolution of imaging is required to make a diagnosis or better characterize the disease, magnetic resonance imaging (MRI) or computed tomography (CT) should be considered. Unenhanced MRI has better resolution than unenhanced CT to detect small cysts. These imaging methods are noninvasive and generally very safe, but CT employs ionizing radiation. The use of intravenous contrast to obtain maximal resolution to see small cysts using CT can be a risk in people with abnormal kidney function. For MRI, occasional patient contraindications include certain implanted devices or retained metal, and possible patient discomfort in the magnet during the study period.

Although the accuracy of different imaging modalities was not systematically reviewed, there is strong evidence that imaging is a reliable means to diagnose or exclude a diagnosis of ADPKD in people at risk with a positive family history. Ultrasound is recommended as the first method of evaluation of a person at risk for ADPKD. For people with a positive family history, specific cyst number and age criteria have been defined to obtain a positive diagnosis and to exclude the diagnosis of ADPKD (Figure 3). These criteria are generally reliable, but apply only to people with PKD1 and PKD2 and may not apply to those with occasional hypomorphic pathogenic variants at these loci. Similarly, diagnostic cyst number/age criteria for a positive diagnosis and exclusion have been described for MRI in people with PKD1 and PKD2 and a positive family history. Similar CT data have not been published, but the 97.5th percentile cyst number/age values for normal people are available. Using imaging to diagnose ADPKD in people with an unknown family history is discussed in Practice Point 1.3.5. In people with equivocal and atypical imaging results, genetic analysis may be helpful.

**Certainty of evidence**

The certainty of evidence was graded as moderate. It is not practical to perform clinical trials to determine the best means to diagnose ADPKD, but several studies involving defined affected and control populations have been performed to develop cyst number criteria to diagnose and to exclude ADPKD. Initial ultrasound criteria for ADPKD-PKD1 were established in 1994, and were updated to the established unified criteria for ultrasonographic diagnosis of ADPKD in people at risk by analysis of a PKD1 and PKD2 population. Overall, these criteria are still considered to be reliable, supporting this recommendation, but the authors identified that the criteria defined for PKD2 did not perform as well for PKD1 with reduced sensitivity due to more false negatives. In addition, the subsequent identification and characterization of additional ADPKD genes and PKD1 hypomorphic alleles mean that these criteria may not be used universally, hence the moderate certainty of evidence grading. In addition to the ultrasound cyst number data, employing MRI analysis of a PKD1 and PKD2 defined population cyst number criteria for a diagnosis and exclusion have been established. These numbers have also been considered reliable, with the new gene and hypomorphic variant provisos indicated above.

**Values and preferences**

There are several issues for the person with ADPKD and their providers to consider when selecting an imaging method. These include the availability and costs of the methods of imaging that differ greatly in different parts of the world, including between high- and low-income countries, but
also between individual high-income counties. Other factors to consider are the resolution needed, for instance, if only small cysts are identified and potential adverse effects, such as radiation exposure for CT from frequent use. Taking these factors into consideration, the Work Group recommends ultrasound as the first method to consider. Ultrasound is the most widely used imaging modality in the evaluation of a person at risk for ADPKD since it is inexpensive, portable, widely available, and does not require contrast or ionizing radiation. However, ultrasound does not offer high enough sensitivity for very small cysts to exclude the diagnosis, especially in young people (<30 years). The low sensitivity is a particular issue for people who are undergoing evaluation as potential kidney donors. Although technology has improved over recent decades with new generation ultrasound machines able to reliably detect cysts of ~5 mm, availability of this new technology is limited. Ultrasound can also be affected by large patient body habitus. Therefore, at-risk young adults should undergo MRI evaluation if the ultrasound results are equivocal since MRI offers superior sensitivity for very small cysts. MRI can detect cysts ≥2 mm in size and the soft tissue contrast is superior to ultrasound or CT. Sensitivity for kidney cysts with CT (including small kidney cysts ≥2 mm in size) is high when i.v. contrast is administered. While it is not the recommended first method for ADPKD screening in at-risk people, it can be useful if other concurrent pathologies are suspected- for example, stone disease, solid kidney mass, kidney hemorrhage, or hydronephrosis.

**Resource use and costs**

Ultrasound, the recommended first test in screening a person at-risk of ADPKD, is the least costly of the discussed modalities (ultrasound, CT, MRI) and the most widely available. The availability and the cost of MRI and CT vary substantially between geographic locations and even institutions within the same country. Therefore, the radiologist providing the care, in consultation with the person at-risk, needs to take these factors into consideration, plus the resolution of imaging needed for the particular person, when ordering an imaging examination. Of particular importance is the consideration of the out-of-pocket expenses not covered by insurance that the person may incur and informing them of such possibilities.

**Considerations for implementation**

The availability of the different imaging modalities is an important consideration when determining how to diagnose ADPKD. While in the high-income countries, ultrasound, MRI, and CT are often available; in low- and middle-income (LMIC) countries, only ultrasound may be available. Also, even if available, costs may influence which tests to employ and in what order. Using ultrasound first allows a diagnosis to be made in most people in most settings. When equivocal results are obtained with ultrasound, follow-up analysis to detect small cysts more reliably can be performed where possible with MRI or CT, depending on the considerations given above, as well as availability and cost. In countries where the cost of an MRI is similar to that of an ultrasound and is readily available, MRI is an excellent alternative for the screening of individuals at risk for ADPKD.
Rationale

It is important that at-risk adults obtain a firm diagnosis of ADPKD, which is the first step toward receiving appropriate care and treatment. As shown in Figure 3, the Work Group recommends using kidney imaging as the first means to diagnose ADPKD in a person at risk (i.e., one with a positive family history [parent, sibling, and/or occasionally a child] diagnosed with ADPKD). Using ultrasound as the first method to screen the individual person and employing the described cyst/number age criteria to determine if the person is affected is generally reliable (Figure 5). In people with bilateral cystic disease and cyst number well above the diagnostic criteria, a positive diagnosis is obtained and frequently no additional imaging or genetic testing is required, although such additional testing may provide prognostic information. If no cysts or very few cysts are found (considering the age of the person), ADPKD can usually be excluded by employing the imaging criteria (Figure 6). If the imaging presentation is atypical, such as unilateral, asymmetric, or a few cysts accounting for a large part of the increased TKV, or if additional clinical features suggest a differential diagnosis, additional imaging and genetic testing may be helpful. In people where a few cysts are found and the diagnosis is unclear, additional imaging may clarify the picture as MRI or contrast enhanced CT are more sensitive to identify small cysts. Genetic testing may also be helpful to clarify if the person has ADPKD. The presentation of the disease in the family should also be considered when interpreting the imaging data in a person at risk.

Incidental discovery of cysts in a person without a known family history of PKD is not unusual, especially with the increasing utilization of imaging for abdominal indications (Figure 4). Imaging of family members (such as parents) can be helpful to determine if cystic disease is present in the family. If positive, follow-up can then proceed as outlined in Figure 3. If the family analysis is negative but the presentation is of multiple bilateral cysts and increased TKV (typical ADPKD), without indications of another form of PKD, a diagnosis of ADPKD can usually be made, although additional imaging and genetic testing may better help define the disease. Imaging and genetic analysis of parents, siblings, and/or adult children may also help to determine if a de novo mutational event has occurred. If the initial results are equivocal or atypical and the initial analysis was by ultrasound, further imaging with MRI or CT, plus genetic analysis, may help to obtain a firm diagnosis. Evidence of abnormal kidney function greater than expected given the cyst burden or atypical extrarenal manifestations may suggest ADPKD due to a minor gene or another cause of cystic disease. In such cases, genetic testing may be helpful to obtain a diagnosis.

The Work Group believes that using imaging to diagnose ADPKD is important to initiate suitable management and treatment of the affected person. Imaging provides not only a diagnosis, but also prognostic information and may identify other disease manifestations, such as severe PLD (Figure 8).

Practice Point 1.3.3: 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 (Figure 5 and Figure 6).
Cyst number and age range data for the diagnosis and exclusion of ADPKD using ultrasound have been determined from an analysis of 577 PKD1 and 371 PKD2 people. Simplified versions of these data are shown in Figures 5 and 6. For a positive diagnosis, the positive predictive value (PPV) is 100% for people with PKD1 and PKD2 based on the defined number of cysts per age category, but the sensitivity is lower, especially in younger people with PKD2, suggesting that follow-up imaging with a more sensitive method and/or genetic testing may be helpful in people <30 years old (Figure 5). For people with an unknown gene type (where genetic testing has not been performed), the ultrasound criteria typically have 100% PPV but variable sensitivity.

For exclusion, the negative predictive value (NPV) of the defined number of cysts for different age categories is also 100% for people over 40 years old with PKD1 and PKD2 but lower for people with PKD2 <30 years old. The specificity is high across all age ranges and genotypes (Figure 6). For people with an unknown gene type (where genetic testing has not been performed), the ultrasound criteria have 91% NPV for those 15–29 years old but higher in older people. Since most of the other genetic forms of ADPKD have milder disease than even PKD2, the exclusion criteria are not reliable for the minor genes. Also, these criteria may not be reliable for weak hypomorphic alleles of the major genes.

Practice Point 1.3.4: For people with a positive family history of ADPKD aged 16–40, the number of cysts seen on MRI have been described to diagnose or exclude ADPKD (Figure 7).
As for ultrasound, analysis of a population of 126 people at risk plus 45 unaffected controls has defined cyst number criteria for people from 16–40 years for the use of MRI. From this study, >10 cysts were adopted as criteria for diagnosing ADPKD and <5 cysts for excluding the disease across the whole age range. This study only analyzed people with PKD1 and PKD2; therefore, these criteria should not be used to exclude ADPKD for the minor genes or for weak hypomorphic PKD1 or PKD2 alleles. Diagnostic criteria for older people are also not available. Of note, the exclusion level was suggested at <10 cysts because one person in a PKD2 family without the pathogenic variant had 10 cysts, but since this study was performed in 2014 before wider ADPKD genetic heterogeneity was described, a minor ADPKD gene as the cause of the cysts was not excluded. Therefore, a more conservative level of <5 cysts is suggested here.

<table>
<thead>
<tr>
<th>&gt;10 cysts total</th>
<th>Sufficient for diagnosis (PPV and sensitivity = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 cysts total</td>
<td>Sufficient for exclusion (NPV and specificity = 100)</td>
</tr>
</tbody>
</table>

Figure 7. Magnetic resonance imaging (MRI) criteria for ages 16-40 years in people with a positive family history.\(^{25}\) NPV, negative predictive value; PPV, positive predictive value.

**Practice Point 1.3.5:** For people with no known family history of ADPKD, kidney imaging plays an important role in the diagnosis of people with detected cysts.

Figure 4 describes the algorithm to follow when cysts are discovered by kidney imaging incidentally. Abdominal imaging should be considered for consenting parents, siblings, and/or adult children to establish if there is a positive family history in which case the scheme in Figure 3 can be followed. If multiple bilateral cysts are identified with increased kidney volume, with or without liver cysts, and no other disease features suggestive of a different cause of kidney cysts, the presumptive diagnosis is ADPKD. If the initial imaging was by ultrasound, follow-up imaging by MRI or CT and genetic testing should be considered to provide prognostic information. If multiple cysts and/or abnormal kidney function and/or extrarenal disease suggestive of another form of PKD are detected, further imaging and genetic testing are indicated (Figure 4).

If only a few incidental cysts are identified without kidney enlargement or liver cysts, there is no clear cutoff for the number of kidney cysts required to make a definite diagnosis. However, the analysis of unaffected people in the populations screened to establish the ADPKD imaging guidelines,\(^{24,25}\) plus analysis of large populations where ADPKD is not suspected, provide some guidance. Detection of one or a small number of simple cysts is not unusual, especially with aging, in people without a known genetic cause of cyst development. In a study of contrast-enhanced CT in 1948 potential kidney donors, 39% had at least one cyst ≥2 mm in the 19–49 years age range and this increased to 63% for people 50–75 years.\(^{54}\) The 97.5th percentile for number of total cysts ≥5 mm was 10 for men and 4 for women in the 60–69-year group; a group of people where an underlying genetic cause is suspected. Therefore, in people with a limited number of cysts and no or
minimal increase in TKV, periodic follow-up (every 5 years) is suggested although more precise imaging (if the initial detection was by ultrasound) and/or genetic testing may clarify the diagnosis.

**Practice Point 1.3.6:** Genetic testing can be helpful to diagnose ADPKD and can provide prognostic information. However, genetic testing is not required to make an initial diagnosis of ADPKD in a person with a typical presentation (Figure 3).

Increasingly, genetic testing is being employed to provide a firm diagnosis and prognostic information in ADPKD (Section 1.4). However, it is not necessary to make a diagnosis by genetics in people with a typical presentation, including those with an uncertain family history. Nevertheless, even in typical ADPKD, genetic testing can provide a definite diagnosis, help with determining the prognosis, and simply enable a diagnosis in other family members. It is also essential for some family planning situations, such as preimplantation genetic diagnosis (Chapter 8). However, genetic testing does not always identify the causative gene, even in people with typical ADPKD. Therefore, negative or equivocal genetic results in a person with typical ADPKD should not be interpreted as the person not having ADPKD, and management, treatment options, and enrollment in clinical trials should not be changed based on the lack of a genetic diagnosis.

**Practice Point 1.3.7:** Genetic testing is particularly informative for people with an equivocal diagnosis based on kidney imaging and in the setting of a negative or unknown family history (Table 2).

Although genetic screening is not required for people with typical ADPKD to obtain a diagnosis, it can provide prognostic information. In addition, there are specific situations where genetic testing can be central to obtaining a clear diagnosis (Table 2). This includes unusually mild or severe disease, people with a negative family history and/or atypical imaging findings, or where there is significant disease variability between family members, suggesting genetic complexity.
### Table 2. Situations where genetic testing can clarify the diagnosis and aid prognosis.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Genetic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited number of cysts</td>
<td>Positive result can show a genetic origin (minor gene or hypomorphic allele)</td>
</tr>
<tr>
<td>Variable disease severity in a family</td>
<td>Mosaicism or biallelic/digenic disease can explain some extreme variability</td>
</tr>
<tr>
<td>Atypical imaging, including asymmetric or unilateral disease</td>
<td>Positive result can show a genetic origin (mosaicism or minor gene involvement)</td>
</tr>
<tr>
<td>Discordance between structural (MIC) and functional (GFR) ADPKD severity*</td>
<td>Genetic testing may reveal an atypical form of the disease or additional genetic or contributory factors. Non-genetic factors may also be important.</td>
</tr>
<tr>
<td>Negative family history</td>
<td>Positive result can show a genetic origin (<em>de novo</em> mutation can be proven)</td>
</tr>
<tr>
<td>VEO-ADPKD</td>
<td>Biallelic disease may be found (Chapter 9)</td>
</tr>
<tr>
<td>Related living transplant donor (&lt;30 years and/or a few cysts detected)</td>
<td>Genetic testing can exclude the familial variant and test for other genetic causes</td>
</tr>
<tr>
<td>Family planning and PGD</td>
<td>Obtaining a genetic diagnosis can aid family planning and enable PGD (Chapter 8)</td>
</tr>
<tr>
<td>All people</td>
<td>Genetics can confirm the diagnosis, identify the responsible gene and variant, and provide prognostic information</td>
</tr>
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</table>

As broad genetic testing becomes more prevalent, incidental genetic finding of a pathogenic variant suggesting ADPKD, in a person/family without known PKD, is increasingly seen.\(^1^8\) In this situation, abdominal imaging is indicated to confirm the genetic diagnosis. If no cysts are detected, segregation of the variant in the family to determine if it occurred *de novo* and to test for possible mosaicism is indicated. For some minor ADPKD genes, like *ALG8* and *PKHD1*, reduced penetrance occurs and so loss of function variants may not always result in cyst development.\(^1^8\,^2^8\) Also, given the mild phenotype associated with single *ALG8* and *PKHD1* pathogenic variants, finding of such a change in a person with typical ADPKD should question if the real (entire) cause of the PKD has been discovered and indicate additional testing.

**Practice Point 1.3.8: Genetic testing can be useful for selection of a living related donor for transplantation, especially if imaging results are equivocal.**

In some situations, a definite diagnosis is required to make clinical decisions, such as for living, related donors. If the potential donor is >40 years old and no cysts are detected by MRI or CT, the imaging analysis alone is sufficient to exclude ADPKD and genetic testing is not required. However, if the imaging data of the prospective donor show some cysts and exclusion of ADPKD is equivocal based on the cyst number criteria and/or if the person is <30 years old, genetic testing can determine if the potential donor has the familial pathogenic variant in genetically resolved families.
In the scenario of just a few cysts being identified in the setting of severe disease resulting in kidney failure in the family, screening a range of PKD genes is more appropriate than just screening for the disease-causing variant, to exclude all known genetic forms of PKD. A few cysts may also be detected by imaging of a prospective donor with no known family history of PKD, and in this case, broad genetic testing is helpful to determine the etiology of the cysts (Figure 4).

**Practice Point 1.3.9:** Genetic testing can be helpful in families with marked phenotypic variability, including very early onset (VEO)-ADPKD or a suspected de novo mutational event.

In situations of unusually intrafamilial kidney disease variability or if a new mutation is likely, genetic testing can reveal complexity explaining the presentations (Table 2). Normally, one pathogenic variant to an ADPKD gene is sufficient to cause ADPKD which is transmitted in a dominant fashion in the family. Although two fully penetrant pathogenic variants to *PKD1* and *PKD2* are not thought to be compatible with a live birth, occasionally, more than one variant has a pathogenic role. One example is biallelic disease, where at least one of the variants is hypomorphic and the pathogenic changes are inherited from the 2 different parents. Indications of biallelic disease are VEO-ADPKD (evident *in utero* or in infancy), but where typical ADPKD is seen in the parental generation and elsewhere in the family (Chapter 9). Sometimes, VEO-ADPKD cases can have an apparent negative family history (mimicking autosomal recessive polycystic kidney disease [ARPKD]) because both of the single hypomorphic alleles found in the people result in no or very mild cyst development (imaging of the parents with MRI or CT is suggested to detect mild disease). Biallelic inheritance can also result in typical, adult-onset disease with an indication of this inheritance being an apparent negative family history and/or marked differences in severity between family members (members with 1 or 2 pathogenic alleles). Digenic disease, where both a *PKD1* and *PKD2* pathogenic allele are present, has rarely been described. Indications of digenic disease can be more than the expected 50% of family members being affected or significant differences in disease severity between family members.

Approximately 20% of families with ADPKD can be traced to a person with a likely de novo mutation. Normally, these new mutations occur in the development of the germ cells (eggs or sperm) and so the offspring derived from these have the new variant in every cell. However, the new mutation can occur after the embryo has formed (such as at the 4-cell stage) and the result is that the person is a mosaic of cells with and without the pathogenic variant. The number of cells with the mutation can range from <1% to ~50% depending on when the mutation occurred, and with different representations of the cell with the pathogenic variant in different organs. Indications of mosaicism are marked phenotypic variability between affected people in different generations in a family that appears to have a de novo mutation in the parental generation or in genetically resolved families with milder disease than expected for the gene/variant type. A recent study of 20 ADPKD families with mosaicism showed all were PKD1. Five families transmitted the variant to the next generation (i.e., the gene was present in the person’s germ cells) and the other 15 were sporadic cases. Overall, the disease was milder in the mosaic case than their offspring or people with a similar pathogenic variant, and the level of mosaicism varied widely. Next generation sequencing (NGS) methods are necessary to detect and quantify the number of cells with the pathogenic variant in mosaic cases.
Mosaicism can be limited to the germ cells, and in this case unaffected parents (no cysts on imaging) can have more than one affected offspring. Although the probability is low, this possibility should be considered when counseling a sibling of an affected person with unaffected parents.

**Practice Point 1.3.10:** Several inherited diseases can clinically mimic ADPKD or ADPLD with kidney and/or liver cysts as part of their phenotype (Figure 8).

Cyst development is a common disease manifestation in the kidney. Although ADPKD is by far the most frequent cause for polycystic kidneys, several mainly inherited disorders can mimic ADPKD or be mistaken for it in certain circumstances (Figure 8). PKD1 and PKD2 encode proteins located on primary cilia and defects in many other genes encoding cilia components can result in cyst development or nephronophthisis (syndromic ciliopathies), but they can normally be differentiated from ADPKD because of the range of pleotropic, extra kidney phenotypes and recessive inheritance. For the X-linked ciliopathy gene, OFD1, a pathogenic variant in females can result in a kidney phenotype closely mimicking ADPKD, but oral, facial, and/or digital abnormalities are usually also present (Figure 8). HNF1β is a transcription factor regulating the expression of many PKD genes and monoallelic variants to HNF1B can occasionally be mistaken for ADPKD, but a range of other kidney, urinary tract, and other abnormalities are most often also present. ARPKD is usually a much more severe, recessively inherited disease than ADPKD with congenital hepatic fibrosis rather than liver cysts, but adult presentations of ARPKD and VEO-ADPKD can result in confusion between the disorders. A few dominant disorders associated with tumor and/or cancer development in the kidney (tuberous sclerosis complex [TSC], Von Hippel-Lindau syndrome [VHL], Birt-Hogg-Dubé syndrome [BHD]) can have kidney cysts as part of their phenotype. Large deletions disrupting the adjacent PKD1 and TSC2 genes, the PKD1/TSC2 CGS, often have VEO-PKD and early kidney failure, but the TSC tumorous phenotypes usually allows the diseases to be differentiated. Single pathogenic variants in the collagen genes, COL4A3 and COL4A4, and in females COL4A5, can result in mild Alport syndrome phenotypes, but kidney cyst can be present. Finally, ADTKD, characterized by small fibrotic kidneys and kidney failure, has similarities to ADPKD-DNAJB11. Because of this wide range of inherited disorders involving cystic kidneys, careful clinical evaluation and often genetic testing can ensure that the correct diagnosis is made.

Noninherited development of kidney cysts can also occur. These include a small number of simple cysts that can develop with aging, and acquired cystic disease, a manifestation that often occurs in kidneys with severe CKD or after kidney failure, especially on long-term dialysis (Table 2). Certain medications, such as chronic lithium usage, can also result in the development of multiple small kidney cysts.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease</th>
<th>Inheritance</th>
<th>Overlapping with ADPKD</th>
<th>Distinguishing from ADPKD</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF1B</td>
<td>HNF1B-related kidney disease</td>
<td>AD</td>
<td>Cystic kidney disease</td>
<td>Congenital kidney and urinary tract anomalies, pancreatic disease, elevated liver enzymes, hyponaguesmia.</td>
<td>Sometimes presents as ADPKD spectrum alone</td>
</tr>
<tr>
<td>AGT, NOTCH2</td>
<td>Alagille syndrome</td>
<td>AD</td>
<td>Kidney cysts</td>
<td>Hepatic bile duct paucity, cholestasis, cardiac, skeletal, facial and eye abnormalities, and dysplastic kidneys.</td>
<td>A major feature can be infanilte, small cystic kidneys and abnormal kidney function</td>
</tr>
<tr>
<td>COL6A1</td>
<td>Hereditary angioathy with nephropathy, aneurysms, and muscle cramps (type IIIA)</td>
<td>AD</td>
<td>Kidney cysts</td>
<td>Hematura, retinal arteriolar tortuosity, muscular contractures, and brain small vessel disease</td>
<td>Presentation with mild cystic disease and few other phenotypes has been described&lt;sup&gt;8,9&lt;/sup&gt;</td>
</tr>
<tr>
<td>COL4A3, COL4A4, COL4A5</td>
<td>Alport spectrum</td>
<td>AD and X-linked</td>
<td>Kidney cysts</td>
<td>Thinning of the glomerular basement membrane, microhematuria.</td>
<td>Occasionally, kidney cysts are the major presentation&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>CYP26A1, SLC24A3, HOGA1</td>
<td>A variety of USD</td>
<td>AR (AD)</td>
<td>Kidney cysts</td>
<td>Predominant phenotype of kidney stones, nephrocalcinosis, and or mineralization</td>
<td>Usually limited cyst involvement&lt;sup&gt;11,12&lt;/sup&gt;; Many apply to other USDs</td>
</tr>
</tbody>
</table>

**ADPKD**

- **MUC1, REN, SLC2A3, UMOD** Autosomal dominant tubulointerstitial kidney disease (ADTKD); AD; Kidney cysts; Reduced kidney function without increased kidney size due to fibrotic kidneys. Cysts, when present, occur late in the disease. No liver cysts; Hyperuricemia (low Furfate) and gout are prominent in ADPKD-UMOD and anemia and gout in ADTKD-REIY.

**Recessive PKD**

- **PKHD1, DZIP1, CTS1** Autosomal recessive polycystic liver disease (ARPKD); AR; Bilateral kidney cystic disease; Typical in utero/infantile presentation of extreme kidney enlargement, but later childhood/adult milder PKD possible. Congenital hepatic fibrosis rather than PKD; Later onset kidney disease can mimic ADPKD, but kidneys usually do not increase in length over time and CHF is usually present.

- **PKHD1, DZIP1, CTS1** Autosomal recessive polycystic kidney disease (ARPKD); AR; Bilateral kidney cystic disease; Typical in utero/infantile presentation of extreme kidney enlargement, but later childhood/adult milder PKD possible. Congenital hepatic fibrosis rather than PKD; Later onset kidney disease can mimic ADPKD, but kidneys usually do not increase in length over time and CHF is usually present.

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**Tumorous disorders**

- **FLCN** Birt-Stamp syndrome; AD; Kidney cysts; Hair follicle hamartomas, kidney tumors, spontaneous pneumothorax, lung cysts; FLCN pathogenic variant described in person with TSC-ADPKD and lung cysts.

- **TSC1, TSC2** Tuberous sclerosis complex; TSC; AD; Kidney cysts; Multisystem disorder with hamartomas in brain, skin, heart, kidneys (angiomylipomas), and/or lung, plus CNS manifestations: epilepsy, learning difficulties, behavioral problems; Kidney cysts can be a major presentation with limited additional phenotypes.

- **PRKD1, TSC2** PKD1/TSC2-Contiguous gene syndrome (CGS); AD; Severe, infantile PKD; Hamartoma and CNS manifestations of TSC; Early onset and severe PKD leading to early death; Mosaicism is common, that may be associated with less severe PKD.

- **VHL** Von-Hippel-Lindau syndrome; AD; Kidney and pancreatic cysts; Familial cancer syndrome with malignant and benign neoplasms in retina, cerebellum, spinal hemangioblastoma, renal cell carcinoma, pheochromocytoma, and pancreatic tumors; Renal cell carcinoma develops from the kidney cysts.

**Ciliopathies**

- **OFD1** Oral-facial-digital syndrome 1; X-linked; Kidney cysts in females; Malformations of the face, oral cavity, including cleft lip and palate, and digits, and PKD with abnormal kidney function. Usually, lethal in males; The PKD can mimic ADPKD, and the facial and digital phenotypes can be minimal.

- **NPHP/other NPHP genes** Nephropathies (NPHP); AR; Cortico-medullary cysts; Childhood presentation with epho-phygosis, loss of cortico-medullary differentiation, small atrophic kidneys, and CKD; NPHP1, and other forms of NPHP, can first present in adulthood.

- **Meval genes** Syndromic ciliopathies such as Joubert, Bardet-Biedl, and Meckel syndrome, and short rib thoracic dystrophy; AR; Kidney cysts; Often infantile or childhood disorders. A wide range of extraneal developmental phenotypes are seen depending on the disorder, including CNS, digital, ocular, skeletal, laterality, and hepatic disease; More than 100 genes associated with syndromic ciliopathies including kidney cysts have been described.

**Acquired disorders**

| None                  | Simple cysts; Sporadic kidney cysts           | Small number, below the cyst number/age range to define ADPKD | The number of simple cysts increases with age |
| None                  | Acquired cystic disease (ACD); Acquired kidney cysts | Usually only seen with severe CKD or after RF. Kidneys are not enlarged | ACD is a risk factor for kidney cancer |

**Figure 8.** Other disorders that present with kidney cysts. AD, autosomal dominant; AR, autosomal recessive; CHF, congestive heart failure; CKD, chronic kidney disease; CNS, central nervous system; RF, renal failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; RCC, renal cell carcinoma.
Practice Point 1.3.11: A targeted next generation sequencing (tNGS) panel or other clinically accredited genetic or genomic test should be employed when performing genetic testing in people with ADPKD.

Obtaining a firm diagnosis in ADPKD is important for the appropriate management and treatment of the affected person. While we do not propose genetic testing for all people, genetic testing is an important part of the armament to correctly diagnose ADPKD. Due to genomic duplication of the PKD1 gene with 6 sequence similar pseudogenes on the same chromosome, the method of locus specific long-range polymerase chain reaction (PCR) and Sanger sequencing has been employed to screen this locus. However, now gene capture and targeted next generation sequencing (tNGS) panels, specifically designed to screen PKD genes, have been shown to be a successful way to screen these genes. These methods are cheaper and easier to use than the Sanger approach and can contain just the known ADPKD genes, a broader array of PKD and ciliopathy genes, or all genes associated with kidney disorders (Figure 8). Even broader approaches, such as WES can be employed (although there were some concerns of PKD1 coverage in WES panels) with analysis initially focused on known ADPKD/PKD genes (PKD gene WES slice). Whole genome sequencing (WGS) is also increasingly being used for clinical genetic screening and has the advantage of even coverage throughout the genome with intronic and inter-gene regions also screened, but cost and data analysis issues need to be considered (Table 3). Currently, a PKD/Nephrology tNGS panel is the most effective and cost-effective means to genetically screen people with suspected ADPKD, and we discourage very limited Sanger or NGS approaches, but we recommend further comparison of the broad based approaches. Increasingly, health insurance companies or government entities paying for testing are covering the costs of the screening with no or limited copay for the patient, although making individual requests is often required. This increased acceptance of genetic testing reflects its perceived value for obtaining a firm diagnosis and aiding the management of the affected person.
<table>
<thead>
<tr>
<th>Factors compared between methods</th>
<th>Sequencing method</th>
<th>Sanger sequencing</th>
<th>Whole exome sequencing (WES) slice*</th>
<th>Whole genome sequencing (WGS) slice*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exons and flanking intronic regions of candidate PKD genes captured and screened by NGS</td>
<td>Targeted next generation sequencing (tNGS) gene panel</td>
<td>All genes (exons) screened separately</td>
<td>Exons and flanking intronic regions of all genes captured and screened by NGS and candidate (PKD or nephrology) genes analyzed</td>
<td>The whole genomic is screened and candidate (PKD or nephrology) genes analyzed</td>
</tr>
<tr>
<td>Exons and flanking intronic regions of candidate PKD genes captured and screened by NGS</td>
<td>Whole exome sequencing (WES) slice*</td>
<td>Long range (LR)-PCR needed to screen the duplicated region of PKD1</td>
<td>Slice can include coding regions of all known PKD and ciliopathy genes (n<del>150) or all known kidney disease genes (n</del>600)</td>
<td>Slice can include genomic regions of all known PKD and ciliopathy genes (n<del>150) or all known kidney disease genes (n</del>600)</td>
</tr>
<tr>
<td>Cost</td>
<td>Least expensive method: Tiny fraction of the genome sequenced and so allows multiplexing for capture and NGS</td>
<td>Price per gene is expensive: The LR-PCR method is time consuming, and difficult</td>
<td>Moderately expensive: Only small fraction of the genome sequenced but less multiplexing options</td>
<td>Expensive: Whole genome sequenced</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Data only obtained from sequenced genes</td>
<td>Data only obtained from sequenced genes</td>
<td>Genes not included in the slice can be retrospectively screened; whole exome screening possible</td>
<td>Genes not included in the slice can be retrospectively screened; whole genome screening possible</td>
</tr>
<tr>
<td>Bioinformatic workload</td>
<td>Moderate number of variants to evaluate</td>
<td>Low number of variants to evaluate</td>
<td>Moderate to high number of variants to evaluate</td>
<td>High number of variants to evaluate</td>
</tr>
<tr>
<td>Hard to screen regions</td>
<td>Coverage optimized for difficult regions, like the PKD1 duplicated area, but some regions still may still be difficult to screen. GC-rich regions may not be adequately screened</td>
<td>Good coverage of GC-rich and duplicated region of PKD1 (with LR-PCR method)</td>
<td>Significant chance that regions with high homology with other regions (PKD1 duplicated region) and GC-rich regions are not adequately screened</td>
<td>More even coverage of the genome, including GC-rich and probably duplicated regions</td>
</tr>
<tr>
<td>Copy number variants (CNV)</td>
<td>CNV detection is possible</td>
<td>Generally, not detected</td>
<td>CNV detection is possible</td>
<td>Most reliable analysis of CNV</td>
</tr>
<tr>
<td>Sequencing method</td>
<td>Mosaicism</td>
<td>Noncoding regions</td>
<td>Guidance</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High read-depth: Mosaic screening possible</td>
<td>Not screened</td>
<td>Best method for primary screening</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not reliably detected</td>
<td>Not screened</td>
<td>Method of choice for variant confirmation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate read-depth: Mosaic screening may be possible</td>
<td>Not screened</td>
<td>Possible for primary screening, with flexibility of the genes screened</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low read-depth: Mosaic screening not reliable</td>
<td>Screened: Deep intronic pathogenic variants detected</td>
<td>Follow-up for high probability cases not resolved by tNGS</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Genetic testing methods for screening for autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPLD). GC, guanine-cytosine; NGS, next generation sequencing; PKD, polycystic kidney disease. *Analysis of the complete WES or WGS as the initial screen is possible but is more expensive, highlights other variants that are unlikely to be relevant, including in reportable genes, and does not greatly increase the change of obtaining a genetic diagnosis.
Practice Point 1.3.12: Clinical genetic testing results should be reported according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Specific ACMG guidelines for reporting variants detected employing NGS approaches have been adopted by clinical testing laboratories. These guidelines consider the nature of the variant, whether it has been previously reported, in silico analysis of nontruncating variants, population data, patient and family information and context, and functional studies to determine the significance of the variant. Possible pathogenic categories are: “pathogenic” or “likely pathogenic” and neutral categories: “benign” or “likely benign”, while ones that do not score appropriately for a diagnostic or benign category are labeled “variants of uncertain significance”. This approach is employed to avoid misdiagnoses based on limited data because of the serious problems associated with misassigned of a monogenic disease diagnosis. The possible consequences of genetic testing and evaluation of variants are shown in Table 4.
<table>
<thead>
<tr>
<th>Person tested</th>
<th>Results of the testing</th>
<th>Significance</th>
<th>Consequence</th>
<th>Follow-up</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical ADPKD presentation (multiple bilateral cysts, kidney enlargement, CKD in older subjects, ± liver cysts); with or without a positive family history</strong></td>
<td>Pathogenic (P) or Likely Pathogenic (LP) variant is detected in a known ADPKD gene</td>
<td>A genetic diagnosis of ADPKD is made</td>
<td>Clinical decisions can be made based on the phenotypic and genetic results</td>
<td>Simple, Sanger testing of at-risk family members. If negative F/H, testing of parents may confirm a de novo mutation</td>
<td>This is the most likely outcome in this situation</td>
</tr>
<tr>
<td></td>
<td>One or more variant of uncertain significance (VUS) is detected in a known ADPKD gene(s)</td>
<td>A genetic diagnosis of ADPKD is not made</td>
<td>The clinical diagnosis should be sufficient to start treatment or enroll in a clinical trial, if warranted by disease severity</td>
<td>Family segregation of VUS may allow reclassification to LP or LB. If negative F/H, testing of parents may confirm a de novo variant; allow the VUS to be reclassified as LP</td>
<td>The existing ACMG guidelines often classify nontruncating variants as a VUS. As new information becomes available reclassification to LP or LB may occur. Research studies may be helpful</td>
</tr>
<tr>
<td></td>
<td>No significant variants are detected</td>
<td>A genetic diagnosis of ADPKD is not made</td>
<td>The clinical diagnosis should be sufficient to start treatment or enroll in a clinical trial, if warranted by disease severity</td>
<td>Consider rescreening of PKD1 by Sanger analysis or WGS. If negative F/H, screen for mosaicism</td>
<td>P/LP variants, especially in PKD1 may be missed by present screening methods. Research studies may be helpful</td>
</tr>
<tr>
<td><strong>Atypical ADPKD presentation (multiple bilateral cysts, no kidney enlargement, no CKD, ± liver cysts); with or without a positive family history</strong></td>
<td>P or LP variant is detected in a known ADPKD gene</td>
<td>A genetic diagnosis of ADPKD is made</td>
<td>Clinical decisions can be made based on the phenotypic and genetic results. Identification of a minor ADPKD gene (and the mild phenotype) may limit treatment and clinical trial options</td>
<td>Simple, Sanger testing of at-risk family members. If negative F/H, testing of parents may confirm a de novo mutation</td>
<td>Obtaining a firm genetic diagnosis occurs less frequently than in those with more typical disease</td>
</tr>
<tr>
<td></td>
<td>One or more VUS is detected in a known ADPKD gene(s)</td>
<td>A genetic diagnosis of ADPKD is not made</td>
<td>PKD without kidney enlargement may limit treatment options and enrollment in clinical trials</td>
<td>Family segregation of VUS may allow reclassification to LP or LB. If negative F/H, testing of parents may confirm a de novo variant; allow the VUS to be reclassified as LP</td>
<td>The existing ACMG guidelines often classify nontruncating variants as a VUS. As new information becomes available reclassification to LP or LB may occur. Research studies may be helpful</td>
</tr>
<tr>
<td>Person tested</td>
<td>Results of the testing</td>
<td>Significance</td>
<td>Consequence</td>
<td>Follow-up</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
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<td>-------------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td>No significant variants are detected</td>
<td>A genetic diagnosis of ADPKD is not made</td>
<td>The mild PKD may limit treatment options and enrollment in clinical trials</td>
<td>Consider rescreening of <em>PKD1</em> by Sanger analysis or WGS. If negative F/H, screen for mosaicism</td>
<td>P/LP variants, especially in <em>PKD1</em> may be missed by present screening methods. Research studies may be helpful</td>
<td></td>
</tr>
<tr>
<td>A P/LP variant is found in another dominantly inherited PKD-related gene</td>
<td>A genetic diagnosis of the implicated disorder is made, if also consistent with re-phenotyping</td>
<td>The new diagnosis may change the management, surveillance, and treatment options of the person</td>
<td>Simple testing of at-risk family members by Sanger sequencing can be performed</td>
<td>This scenario is found at a relative low level</td>
<td></td>
</tr>
</tbody>
</table>

*Table 4. Consequences of genetic testing by targeted next generation sequencing (tNGS) for people with autosomal dominant polycystic kidney disease (ADPKD).* AMCG, American College of Medical Genetics and Genomics; F/H, family history; LB, likely benign; LP, likely pathogenic; P, pathogenic; VUS, variant of uncertain significance; WGS, whole genome sequencing
Practice Point 1.3.13: Genetic testing is not always definitive in a person with ADPKD caused by mutations in *PKD1* or *PKD2* because screening methods do not detect all pathogenic variants and some variants are not classed as pathogenic using ACMG guidelines.

Clinical genetic testing in a person with ADPKD does not detect all pathogenic variants (probably ~75%\(^\text{18}\)) and further study should be performed to determine the yield of obtaining a genetic diagnosis from this testing. Although most pathogenic changes are in the coding exons and flanking splicing regions some changes are deep within introns or in gene regulator regions that may not be screened by exon-based tNGS or WES approaches, although they should be covered by WGS. In addition, some variants may be classed in the nondiagnostic VUS grouping.\(^\text{45}\) ADPKD is highly allelically heterogeneous with more than 2000 different pathogenic variants reported in the known genes,\(^\text{92, 93}\) with new variants that have not previously been described often identified. For novel truncating changes, classification using the ACMG guidelines will normally place them in a pathogenic category.\(^\text{45}\) However, for novel nontruncating changes, which represent ~35% of *PKD1* pathogenic variants,\(^\text{5}\) the variant is often classed as a VUS. In some cases, showing coinheritance with the disease by segregating the variant in family members can allow reclassification to a diagnostic group. Functional studies can also be helpful, but few are presently available for the ADPKD genes. More variant reporting in databases, such as ClinVar or the ADPKD Variant Database, can also help to reclassify VUS to diagnostic categories. More research is needed to improve the number of variants obtaining a diagnostic categorization by making specific ACMG guidelines for the ADPKD genes.

Practice Point 1.3.14: In a person with ADPKD and with a typical presentation, negative or uncertain genetic results do not exclude an inherited form of ADPKD.

As discussed above, genetic testing does not identify, or define as pathogenic, all significant variants in the ADPKD genes using the existing methods and evaluation guidelines. Therefore, in a person with a typical ADPKD presentation, if genetic testing does not detect a pathogenic class variant, for instance, only VUS are defined, this should not be interpreted as the person not having ADPKD. Therefore, management, treatment, and access to clinical trials should not be altered by these findings and should proceed as for any clinically defined person with ADPKD.

Practice Point 1.3.15: In a person with ADPKD and atypical imaging or another unusual presentation, negative or uncertain genetic results do not exclude an inherited form of PKD.
For people with just a few cysts or an atypical imaging or extrarenal presentation, negative/VUS findings should not be interpreted as there being no genetic cause of the kidney cysts, and management should proceed based on the clinical findings.

**Practice Point 1.3.16: In a family with a known gene variant, screening for the specific variant (Sanger sequencing) is usually sufficient to diagnose or exclude ADPKD or to determine affected status.**

We have advised to use tNGS or a WES slice for screening of people with suspected ADPKD, but once the variant is defined within a family, Sanger analysis of just the pathogenic variant in at risk family members that wish to be screened is usually sufficient to determine if they are affected (employing a long-range PCR approach for PKD1). This means that obtaining additional diagnoses within genetically characterized families can be rapidly performed and is inexpensive. The exception would be the person in a family with a very different phenotype than seen in other family members, for instance a limited number of cysts in a family with typical ADPKD and kidney failure, and vice versa, where the normal primary NGS screening should be performed.

**Research recommendations**
- A study comparing Sanger, tNGS, WES, and WGS on a control population would be of value to highlight the strengths and weaknesses of each approach.
- Studies are needed to determine the yield more clearly from genetic testing.
- Research is needed to improve the ACMG guidelines for the ADPKD genes to reduce the number of variants placed in the non-diagnostic category of VUS.

**1.4. Prognostics**

**1.4.1. Factors associated with the severity of kidney disease in ADPKD**

ADPKD is typically an adult-onset kidney disease with kidney failure (average age at onset of ~60 years) as a common outcome. However, wide divergences from this typical outcome have been documented, from fetal demise to people with normal kidney function into old age. Extrarenal manifestations, such as the occurrence of severe PLD and of intracranial aneurysms (ICA) are also highly variable. The severity of kidney disease is governed by factors specific for PKD and others associated with CKD progression, as illustrated in Figure 9. These factors may influence the rate of cyst initiation, alter the rate of cyst expansion, and/or influence the rate of destruction of normal kidney tissue, and should be discussed with the patient in counseling. Both the gene involved (genic affect; Practice Point 1.4.1.1), and for PKD1, the type of pathogenic variant (allelic effect), especially whether it is predicted to truncate the protein product influences the severity of kidney disease (Figure 9; Practice Point 1.4.1.2). However,
significant intrafamilial variability in kidney disease severity indicates factors beyond the causative disease variant are important.\textsuperscript{97, 98}

![Figure 9. Factors associated with the rate of disease progression in autosomal dominant polycystic kidney disease (ADPKD).](image)

In unusual situations, such as the \textit{PKD1}/\textit{TSC2} CGS\textsuperscript{77, 78} and \textit{PKD1}/\textit{PKD2} digenic disease,\textsuperscript{62} plus in animal models and rare cases,\textsuperscript{59, 99, 100} pathogenic germline variants in other genes have been shown to influence the severity of the ADPKD-associated kidney disease. However, to what extent genetic variants in other genes, both rare and common, influence the severity of disease in typical ADPKD is not known. Likewise, biallelic disease has been clearly demonstrated as a cause of VEO-ADPKD,\textsuperscript{32, 58, 60, 61} but whether minor variants in the normal copy of the disease-causing gene influence the severity of kidney disease more generally is not clear. There is also good evidence that somatic variants to the normal allele of the disease-causing ADPKD gene occur and possibly somatic changes elsewhere,\textsuperscript{101-104} but whether the variability of the timing or frequency of these somatic genetic events alters the severity of the PKD is not known.
The factors that influence the rate of progression of CKD generally are important in ADPKD, including the sex of the affected person, body habitus, and salt intake (see also Chapter 4). Smoking is generally discouraged because of its multiple adverse effects on health, while exercise is normally encouraged (see Chapter 7), but currently available experimental data on kidney disease progression do not allow clinical conclusions. Caffeine intake has been discouraged specifically in ADPKD, but the evidence supporting a detrimental effect on kidney disease progression is limited or mainly restricted to animal models. In animal models, kidney damage is a major factor influencing the rate of kidney disease progression, however, the importance of acute kidney injury (AKI) to human disease progression has not been systematically studied. Likewise, there are limited data on the role of comorbidities (e.g., diabetes) or vascular-related changes to disease progression.

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

As we have described in Section 1.1., several different genes can cause ADPKD, each of which is associated with a typical presentation. However, the presentation and progression are variable between and within families, and there are limited data about many of the minor genes involved. For the major genes *PKD1* and *PKD2*, PKD1 is consistently associated with more severe kidney disease than PKD2. The median age at kidney failure was 54.3 y (95% confidence interval [CI]: 52.7–55.9 y) and 74.0 y (95% CI: 67.2–80.8y), for PKD1 and PKD2, respectively, in a study of European families, 58.1 y (95% CI: 56.5–59.9 y) and 79.7 y (95% CI: 76.8–82.6 y) in genetically resolved Genkyst pedigrees, and 58.0 y and 74.8 y in a sequence characterized Mayo Clinic population. Other measures of severity of kidney disease, including estimated glomerular filtration rate (eGFR)/age and height-adjusted TKV (htTKV)/age are greater and smaller for PKD2 compared to PKD1, respectively.

For the minor ADPKD genes, the greatest risk of kidney failure is with ADPKD-NEK8, with people who are affected reaching kidney failure in childhood (1-17 years), and milder course of the disease reported with certain alleles in case of mosaicism. It is important to mention that only specific variants of the kinase domain of *NEK8*, especially the recurrent variant p.Arg45Trp, were shown to cause ADPKD-NEK8. Heterozygous loss-of-function variants of *NEK8* are not expected to lead an ADPKD phenotype. In ADPKD-DNAJB11, a study of 77 affected people (23 pedigrees) found a median age at kidney failure of 75 y (range: 55-89 y). More limited data are available for the other ADPKD genes, but that data indicate a moderate risk of kidney failure for ADPKD-ALG9 and ADPKD-ALG5, and a low risk for ADPKD-ALG8, ADPKD-GANAB, ADPKD-IFT140, and ADPKD-PKHD1. Disease penetrance appears low for ADPKD-ALG8 and ADPKD-PKHD1, so that people with loss of function variants may have limited or no kidney cysts, while data about the penetrance of
ADPKD-ALG9 and ADPKD-ALG5 and other minor genes are limited.\textsuperscript{18, 28} Therefore, knowing the affected gene is of value when assessing the risk of kidney failure in ADPKD, but the true phenotypic range and penetrance is unknown for many minor genes.

**Practice Point 1.4.1.2: In PKD1, the type of PKD1 mutation influences the severity of kidney disease.**

At a population level, pathogenic variants that are predicted to truncate the encoded protein compared with nontruncating are associated with worse kidney outcomes. The Genkyst study found the median age at kidney failure was 55.1 y (interquartile range [IQR]: 48.5–62.1 y) for \textit{PKD1} truncating and 65.8 y (IQR: 53–76.5 y) for \textit{PKD1} nontruncating variants.\textsuperscript{30} However, the nontruncating group is heterogeneous, including inactivating variants and hypomorphic variants generating some function protein. Efforts to separate these groups by \textit{in silico} studies into predicted more penetrant and less penetrant found median ages at kidney failure of 60.8 y and 66.2 y, respectively.\textsuperscript{5, 95} Multivariate analysis also including MIC, sex, baseline eGFR, and baseline body mass index (BMI) showed the hazard ratio (HR) for the risk of kidney failure during follow-up was 0.42 (95% CI: 0.252–0.699) for the least penetrant PKD1 group, and 0.273 (95% CI: 0.150–0.497) for PKD2 relative to PKD1 truncating, but the more penetrant nontruncating PKD1 group were not significantly different. In the largest study of PKD2, nontruncating variants were associated with a higher eGFR than truncating.\textsuperscript{113} Therefore, the type of pathogenic variant to the major genes is significant to future kidney outcomes, however, there is considerable variability at the level of the affected person. For prognostic predictions, we advise employing genotype data with clinical indications in the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) Score\textsuperscript{30}.

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

The severity of disease progression in other family members, such as the age at kidney failure, provides some guidance to the likely outcome in other, including presymptomatic, affected family members.\textsuperscript{114} This is expected as usually all affected family members will share the same pathogenic variant. However, because of significant intrafamilial variability related to genetic-modifying factors and differences in lifestyle and environment exposures, this guidance is only moderately predictive.\textsuperscript{97, 98} Significant differences in disease presentation between affected family members, such as VEO-ADPKD, may indicate genetic complexity and represent an indication for genetic testing.

**Practice Point 1.4.1.4: Male sex is a prognostic factor of more severe disease in people with ADPKD with males generally having larger kidneys for age than females and progressing to kidney failure at approximately 5 years earlier than females.**
Data on the importance of sex to the severity of ADPKD kidney disease are somewhat variable but generally male sex is associated with more severe disease. In Genkyst and Mayo Clinic studies, the age at kidney failure was 62.8 y or 58.2 y and 65.4 y or 63.9 y for males and females, respectively.\cite{29} Corresponding males and females ages were, 55.7 y and 59.4 y for PKD1, and for PKD2, 71.2 y and <50% of females experienced kidney failure.\cite{95} In univariate analysis, male sex was associated with a greater risk of kidney failure (hazard ratio [HR]: 1.3; 95% CI: 1.0–1.4) and HR: 1.59; 95% CI: 1.27–2.0).\cite{95} In multivariate analysis that also considered age, mutational group, baseline eGFR, and BMI, the kidney failure HR for males relative to females was 1.41 (95% CI: 1.09–1.81).\cite{95} We suggest considering sex when determining outcomes and advise using it as part of PROPKD score.

**Practice Point 1.4.1.5: Overweight and obesity are risk factors for faster progression of ADPKD.**

In animal models, low-calorie and specific diets, including high water intake, have reduced the rate of kidney disease progression,\cite{115-118} but the importance of these factors to the human disease is still being investigated. Relatedly, obesity is a risk factor for the development and progression of CKD, but there are limited data about its significance in ADPKD. In the HALT Progression of Polycystic Kidney Disease (HALT-PKD) Study A population, BMI categories (with kidney and liver weight removed) of normal (18.5–24.9 kg/m$^2$), overweight (25–29.9 kg/m$^2$), and obese (>30 kg/m$^2$) were associated with annual mean percentage (standard deviation [SD]) rates of hTKV growth of 6.1% ± 64.7%, 7.9% ± 64.8%, and 9.4% ± 66.2%; p=0.001, respectively.\cite{119} In a multivariate model, the beta annual mean percentage (95% CI) increase of hTKV growth for obese compared to normal was 2.70% (95% CI: 1.45–3.95), and the beta of annual eGFR decline was -0.08 (95% CI: -0.15 – -0.02). In a Mayo multivariate analysis, the HR for kidney failure during follow-up for a 5 kg/m$^2$ greater BMI was 1.119 (95% CI: 1.004–1.248); p=0.042.\cite{95} Overall, there is modest evidence that body weight is associated with the rate of disease progression in ADPKD.

**Practice Point 1.4.1.6: Higher salt intake is associated with faster progression of ADPKD.**

In HALT-PKD Study A, using a linear mixed model, a significant association of average urine sodium excretion (UNaE) and annual rate of TKV growth (0.43%/year for each 18-mEq increase in UNaE; p<0.001) was observed.\cite{120} Using a similar model in HALT-PKD Study B, a greater annual rate of decline in eGFR was associated with salt intake (–0.086 ml/min/year for each 18 mEq/24 h increase in UNaE; p < 0.001). Also, a HR=1.083 for each 18 mEq/24 hour increase in UNaE was seen for reaching the study endpoint (50% reduction from baseline eGFR, kidney failure, or death) using a Cox proportional hazards model (p= 0.01). In a Netherlands study, salt intake was significantly associated with annual change in eGFR of -0.11 ml/min per
1.73 m² (95% CI: 0.20 – 0.02) per gram of salt.\textsuperscript{121} Therefore, controlling salt intake may be of value in ADPKD.

1.4.2. Ways to assess the severity of kidney disease progression

There are several different ways to monitor the severity of kidney disease in ADPKD and potentially identify people with more rapid progression (Figure 10). ADPKD is a disease that normally progresses over many decades with kidney failure typically occurring later in life. Since measurements of kidney function, such as eGFR determined from serum creatinine (SCr), are relatively insensitive to detect small reductions in function, other methods to monitor early-stage disease have been developed. From the results of the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study, measuring the size of the kidneys by MRI and determining hTKV has proven the best biomarker in the early disease stages.\textsuperscript{122} We therefore advise employing hTKV for prognostic purposes in early ADPKD. A simple way to employ hTKV is using the MIC which provides age-adjusted categories and helps to identify patents with rapidly progressive disease (Recommendation 1.4.2.1).\textsuperscript{26} Analysis of kidney function can, however, also be helpful as a prognostic marker and so we advise monitoring kidney function as eGFR/age or as the slope of eGFR decline (Practice Point 1.4.2.7). Early onset of ADPKD disease manifestations, such as hypertension and urological events, can also have predictive value. The PROPKD score combines genetic and sex data with details of early onset of disease symptoms to provide prognostic information (Practice Point 1.4.2.8).\textsuperscript{30} Other factors that may be helpful to help identify rapidly progressive people are urine and serum biomarkers (Practice Point 1.4.2.10). Decreased renal blood flow (RBF) has been shown to be an early marker of severity of kidney disease but is difficult to use and calibrate, and we feel at this time that further research is required.\textsuperscript{123, 124} Identifying and utilizing genetic-modifying factors, including as a polygenic risk score, may also have predictive value. Ultimately, it is likely that a model that includes several of these factors will have greater predictive power than the individual methods for assessing disease severity, but at this stage this is still to be developed.
Figure 10. Methods to assess the rate of kidney disease progression in autosomal dominant polycystic kidney disease (ADPKD). BP, blood pressure; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume; hem; hematuria; MIC, Mayo Image Class; NT, nontruncating; PKD, polycystic kidney disease; PROPDKD, Predicting Renal Outcome in Polycystic Kidney Disease; RBF, renal blood flow; T, truncating; uβ2MG, urinary beta-2 microglobulin; uKIM1/Cr, urinary kidney injury molecule-1 to creatinine ratio; uMCP1, urinary monocyte chemoattractant protein-1; U/P, urine-to-plasma; UTI, urinary tract infection; ↑, increase in value associated with outcome; ↓, decrease in value associated with outcome.

**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.

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

While TKV can be measured by ultrasound, CT, or MRI, MRI is most strongly advised for prognostics due to its accuracy, reproducibility, and safety for TKV determination. MRI is noninvasive, does not use ionizing radiation, provides high soft tissue contrast, and does not need i.v. contrast (gadolinium-based contrast agents) for TKV calculation. These advantages are
balanced by cost and availability. CT is another option that is as accurate as MRI, but ionizing radiation is employed.\textsuperscript{125}

TKV can be measured with the ellipsoid equation ($\pi/6 \times L \times W \times D$), that requires sagittal and coronal length (L), width (W), and depth (D) data.\textsuperscript{26} While convenient and rapid, it makes geometric assumptions about the kidney shape and so is less accurate for the unpredictable shapes of the ADPKD kidney, although a reasonable TKV estimate can be determined.\textsuperscript{26} Other ways to determine TKV using MRI include volume calculation by stereology,\textsuperscript{126} planimetry tracings,\textsuperscript{127, 128} semiautomated,\textsuperscript{129} and fully automated approaches.\textsuperscript{130} Methods that allow actual organ segmentation are more precise, with automated and semiautomated methods favored because of the time needed for TKV measurement and accuracy. Programs for automated and semiautomated analysis are now widely available.

Dividing the TKV by the person’s height in meters (htTKV) is favored as it partially corrects for differences in kidney size due to height.\textsuperscript{131}

Practice Point 1.4.2.5: Ultrasound-determined TKV and kidney length measurements also have prognostic value.

ADPKD is most often characterized by exponential kidney enlargement due to an increase in cyst number and size that results in irreversible renal parenchymal damage. While kidney enlargement varies between people with ADPKD, data indicate that it is at a relatively consistent rate over time for a given affected person, as shown by the CRISP study.\textsuperscript{122} In 214 participants, the mean (± standard deviation [SD]) baseline TKV was 1060 ± 642 ml and increased by 204 ± 246 ml (5.27 ± 3.92%/year; p<0.001) over 3 years follow-up. A similar rate of increase of 5.5%/year (95% CI: 5.1–6.0) was found in the placebo group of the Tolvaptan Phase 3 Efficacy and Safety Study in ADPKD (TEMPO 3:4) clinical trial.\textsuperscript{22} In the initial description of the CRISP results, larger kidneys were associated with a decline in kidney function; subjects with a baseline TKV >1500 ml had a mean GFR decline of -4.33 ± 8.07 ml/min/year; p<0.001) while subjects with a baseline TKV 750-1500 ml had a mean GFR decline of (−0.69 ± 9.47 ml/min/year; p= 0.57).\textsuperscript{122} In the latest follow-up of the CRISP population, the OR per 100 ml/m increment in baseline htTKV of reaching CKD G3, G4, or G5D during 13 years of follow-up was 1.38 (95% CI: 1.19–1.60), 1.42 (95% CI: 1.23–1.64), and 1.35 (95% CI: 1.18–1.55), respectively.\textsuperscript{132} The systematic analysis of htTKV data collated for this guideline found a consistently higher risk of worsening kidney function (e.g., GFR slope or incident CKD G3) in subjects with a greater htTKV/age (Supplementary Table S2). Hence, kidney size, even from an early disease stage has strong predictive value for determining later declines in kidney function and kidney failure. Since the significance of htTKV is highly age dependent, this data alone can be difficult to interpret, therefore, htTKV/age groups have been defined to categorize people with ADPKD into MIC.\textsuperscript{26}
**Recommendation 1.4.2.1:** We recommend employing the Mayo Imaging Class (MIC) to predict future decline in kidney function and the timing of kidney failure (*IB*).

This recommendation emphasizes the value of using htTKV categorized by MIC as a prognostic measure to determine future declines in kidney function and to approximate the age at kidney failure in people with ADPKD. There is moderate evidence to support this recommendation.

**Key information**

*Balance of benefits and harms*

A convenient way to use htTKV data to identify people with rapidly progressive disease is to employ the MIC. The study of Irazabal *et al.* defined 5 typical imaging classes (1A to 1E) based on the annual htTKV growth rate (1A: <1.5%; 1B: 1.5%–3%; 1C: 3%–4.5%; 1D: 4.5%–6%; or 1E: >6%), starting from a theoretical equal htTKV at birth (Figure 12). Hence, 5 htTKV groups are defined for classifying the size of the kidneys for people from 15–80 y with typical radiologic presentations. Importantly, atypical radiological presentations (MIC 2), such as unilateral, segmental, asymmetric, or lopsided (MIC 2A) or atrophic (MIC 2B) are excluded from the predictive rubric since the predictive nature of the MIC likely does not apply in these special situations (Figure 11). Likewise, the MIC should only be used for people affected by PKD1 or PKD2. The MIC can be calculated using a web-based application ([https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754](https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754)).

The application was developed as a research tool that allows MIC calculation based on kidney size measures from MRI or CT or kidney volume estimated from stereology, together with patient height and age. The addition of present SCr and demographic information can also allow approximate, future eGFR values to be estimated.
<table>
<thead>
<tr>
<th>Class, subclass, and term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Typical ADPKD</strong></td>
<td>Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV</td>
</tr>
<tr>
<td><strong>2. Atypical ADPKD</strong></td>
<td><strong>A Unilateral</strong></td>
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<tr>
<td></td>
<td><strong>Segmental</strong></td>
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<tr>
<td></td>
<td><strong>Asymmetric</strong></td>
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<td></td>
<td><strong>Lopsided</strong></td>
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<tr>
<td><strong>B</strong></td>
<td><strong>Bilateral presentation with acquired unilateral atrophy</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Bilateral presentation with bilateral kidney atrophy</strong></td>
</tr>
</tbody>
</table>

**Figure 11.** Mayo Imaging Classification (MIC) of people with autosomal dominant polycystic kidney disease (ADPKD) by prespecified imaging findings. TKV, total kidney volume. Reproduced from Irazabal et al.²⁶

**Figure 12.** The Mayo Imaging Classification (MIC) divides height-adjusted total kidney volume (htTKV)/age into 5 difference classes.²⁶ htTKV plotted against age is divided into 5 groups, 1A to 1E, reflecting kidney size and related to the severity of the kidney disease. Starting at theoretical starting value of 150 ml/m², annual htTKV growth rates are: <1.5% for 1A; 1.5–3.0% for 1B, 3.0–4.5% for 1C, 4.5–6.0% for 1D, >6.0% for 1E
Prognostic information in ADPKD is helpful for the affected person and their nephrologist to ensure that the care provided is based on the best estimates of the severity of the kidney disease and to estimate if kidney failure is likely and the approximate timing of this event. This ensures that approaches prior to kidney failure, such as preemptive transplantation, are considered in a timely way. There is strong evidence that hTKV is the best existing prognostic biomarker in ADPKD and calculating the MIC is the easiest and simplest means to interpret and employ that data. MIC also excludes people with atypical kidneys where the relationship between hTKV/age and more rapid progression may not hold. Abdominal imaging performed by MR or CT is needed to calculate the MIC. These imaging methods are noninvasive and generally very safe, and gadolinium is not necessary in the MRI calculation of hTKV, however contraindications that occur occasionally for MRI include certain implanted devices or retained metal and possible patient discomfort in the magnet during the study period.

**Certainty of evidence**

The certainty of evidence was graded as moderate. Five studies (in 6 articles) reported various multivariable analyses that evaluated MIC as a predictor of future kidney function (>4 years) as measured by eGFR slope or development of kidney failure (Supplementary Table S2). The studies conducted mostly adequate multivariable analyses (based on analytic methods and small loss to follow-up). Four of the 5 studies reported statistically significant associations between baseline MIC and future kidney function, with mostly stronger associations between higher MICs compared with lower MICs. The certainty of evidence was downgraded from high to moderate based primarily on some inconsistencies regarding how strongly each of the MICs was associated with change in kidney function.

From the initial study, the estimated frequency of kidney failure after 10 years follow-up increased for each baseline MIC (A to E): 2.4%, 11.0%, 37.8%, 47.1%, and 66.9%, respectively. The study of Lavu et al. analyzed MIC as part of a multivariate analysis and the risk of reaching kidney failure at any point during follow-up (average follow-up of 16.8 y) was 97%, 92%, 78%, and 71% less for MIC 1A, 1B, 1C, and 1D subjects, respectively, compared to MIC 1E. Consistent data were found in smaller studies with a shorter period of follow-up. This recommendation is also supported by data about the age at kidney failure for people in the different MICs. For instance, in an analysis of 1079 people with PKD1 or PKD2, the Kaplan Meier determined age at kidney failure was 45.1 y, 55.6 y, 62.8 y, 71.2 y for MIC 1E to 1B, respectively, with <20% of MIC 1A people experiencing kidney failure.

Analysis of trajectories in the CRISP cohort showed a wide range of rates of decline based on the MIC (more rapid with higher class) and with age (tending to increase with age, consistent with a nonlinear decline for most classes) (Figure 13). In similar analysis of a Mayo population where more linear declines were modeled for the more severe MIC and genotypic
groups, the increase in rate over time was also seen but was not evident in the most severe MIC group (1E).95

<table>
<thead>
<tr>
<th>Predicted parameter</th>
<th>Age (yr)</th>
<th>20–30</th>
<th>30–40</th>
<th>40–50</th>
<th>50–60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A GFR Slope</td>
<td></td>
<td>109 (95–123)</td>
<td>110 (99–121)</td>
<td>97 (83–110)</td>
<td>69 (49–90)</td>
</tr>
<tr>
<td>Class B GFR Slope</td>
<td></td>
<td>113 (106–120)</td>
<td>108 (103–113)</td>
<td>89 (82–96)</td>
<td>56 (45–67)</td>
</tr>
<tr>
<td>Class C GFR Slope</td>
<td></td>
<td>113 (107–119)</td>
<td>101 (96–106)</td>
<td>75 (68–82)</td>
<td>35 (24–45)</td>
</tr>
<tr>
<td>Class D GFR Slope</td>
<td></td>
<td>119 (112–125)</td>
<td>92 (87–98)</td>
<td>51 (44–59)</td>
<td>–3.23 (–15.73–9.26)</td>
</tr>
<tr>
<td>Class E GFR Slope</td>
<td></td>
<td>103 (97–110)</td>
<td>64 (57–71)</td>
<td>10 (0–21)</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 13. Predicted glomerular filtration rate (GFR) values, slopes, and paired differences between predicted and observed GFR at different ages using a polynomial model. Adapted from Yu et al. 2020. Units of GFR are ml/min per 1.73 m² (95% confidence interval); slopes are ml/min per 1.73 m² per year. GFR – predicted GFR; positive means underestimated. yr, year

Values and preferences

The MIC requires CT or MR imaging and determination of htTKV. Measurement of htTKV by automated or semiautomated methods is strongly recommended due to accuracy, reproducibility, and speed. However, these methods require specific software and there is presently a lack of availability at some locations, although this has continued to improve. The ellipsoid equation can be used to estimate htTKV from MR or CT determined kidney size measurements, but it is less accurate than segmentation approaches.138 Ultrasound, which is more widely available, can also be used for htTKV calculations, but these are generally not as accurate as MR or CT determined values.

Considerations for implementation

The availability of the methodology is an important consideration when estimating outcomes in ADPKD. While in high resource settings MRI and CT are generally available, in low resource settings only ultrasound may be available. Also, even if available, costs may influence which tests to employ and in what order. Therefore, it is important to use the appropriate and available technology to obtain images based prognostic information in ADPKD. Images may be repeated annually or up to 5-year intervals depending on the clinical setting. For example, small differences in htTKV in a young person may have a large effect on the image classification. Repeating the measurement of htTKV after 1 year can provide assurance that the
image classification was correct. In most cases, lacking other indication, imaging studies can be obtained less frequently (e.g., every 3–5 years).

Rationale

Calculating the htTKV from MR or CT abdominal imaging allows determination of the MIC which in turn provides the most reliable prognostic information for the affected person. This analysis will determine if the person has a typical or atypical imaging pattern, and for typical people, their MIC (A–E). There is strong evidence that the MIC is correlated with future decline in kidney function and timing of kidney failure. The MIC calculator, with the addition of SCr and basic demographic data also allows future eGFR values to be estimated. This categorization can be used to select subjects for clinical trials and may help to determine the best treatment options for people with ADPKD, including tolvaptan (see Chapter 4).

Practice Point 1.4.2.3: When using the MIC for prognostics, exclude people with atypical imaging patterns (Class 2A and 2B) as htTKV does not predict kidney outcomes in these people.

Atypical (or Class 2) ADPKD includes affected people who present with unilateral, segmental, asymmetric, or bilateral atypical presentation; MIC 2A, and people with acquired unilateral or bilateral kidney atrophy; MIC 2B (Figure 1426). Prognostic predictions of the MIC are not applicable in people with these atypical imaging patterns because atrophy (MIC 2B) can be associated with abnormal kidney function without enlargement, and kidney enlargement due to just a few large cysts (MIC 2A) usually leaves sufficient functioning parenchyma for the kidney function to be normal.

Practice Point 1.4.2.4: When using the MIC to predict future kidney function, it is important to exclude people who have pathogenic variants in genes other than PKD1 or PKD2 as the predictions are likely unreliable in these people.

The MIC was mainly developed in a population of people with PKD1 and PKD2 or genetically uncharacterized but with typical disease and, therefore, not designed to assess people with ADPKD due to pathogenic changes in the minor genes. Often people from this group are classed as atypical because just few cysts large cysts account for the kidney enlargement (MIC 2A; e.g., IFT14010) or significant fibrotic atrophy (MIC 2B) is seen (e.g. DNAJB118,21 or ALG511). However, even if people with minor gene pathogenic variants are classed as typical (MIC 1A–E), the MIC predictions should not be considered reliable in these cases. If no genetic information is available and the kidneys are classified as typical (MIC 1A–E), the MIC predictions can be applied in these situations.

Practice Point 1.4.2.5: Ultrasound-determined TKV and kidney length measurements are less precise than measurements using MRI segmentation, but also have prognostic value.
Ultrasound measurement of TKV in people with ADPKD in CRISP were found to be inaccurate compared to MRI and were considered to lack the precision necessary to measure short-term disease progression, such as in clinical trials. However, ultrasound did provide an estimate of TKV that reflected the severity of kidney disease in an individual person. An analysis comparing kidney size (both htTKV and kidney length >16.5 cm) measured by ultrasound and MRI as a predictor of progression of future decline in GFR showed similar area under the curve (AUC) values from receiver operator curves (ROC) for predicting eGFR decline to CKD G3 with both measurements and modalities. However, the authors did not assess the difference in test accuracy between the 2 measures. More recently, ultrasound ellipsoid measurements were found to underestimate TKV by 11% and to misclassify the Mayo Clinic imaging class (more frequently to a lower class) in 22% of patients, compared with MRI manual segmentation. Nevertheless, they predicted high-risk Mayo Clinic imaging classes (1C–1E) with a positive predictive value of 98%, specificity of 99%, negative predictive value 95%, and sensitivity of 94%. An average ultrasound kidney length >16.5 cm was highly predictive of Mayo Clinic imaging classes 1C–1E only in patients aged ≤45 years and misclassified some patients with rapid disease progression. Therefore, ultrasound data may be used to estimate the severity of the ADPKD but are less precise than MRI or CT based segmentation measurements which should be used in preference where available and in cases of doubt. See also Chapter 9 for use of ultrasound for disease assessment in children.

**Practice Point 1.4.2.6: Advanced MRI-based biomarkers may provide additional predictive value.**

While htTKV (MIC) is presently the best biomarker in ADPKD for predicting future decline in kidney function, it does not take advantage of the wealth of information provided by MRI about the composition of the kidney. Several studies in the past few years have shown value in this data. Kline et al. showed that addition of texture analysis (specifically entropy, correlation, and energy) to a prediction model improved the prediction of CKD G3a, G3b and 30% decline after 8 years of follow-up. Bae et al. analyzed htTKV after excluding the volume of exophytic cysts for people with both MIC 1 and 2 and showed improved predictive performance compared with standard htTKV for developing CKD G3 during follow-up. This method may allow some people with MIC 2A to be assessed by the adjusted MIC. Riyahi et al. found that the number of hemorrhagic cysts detected in MRI improved prediction of future eGFR compared to htTKV alone (p=0.045). Recently, techniques have been developed to individually segment cysts and quantify additional MRI derived biometrics. In a study of CRISP participants, total cyst number and cyst parenchyma surface area showed superior prediction of the slope of eGFR decline, kidney failure, and CKD G3a, G3b, and G4, compared to TKV.
When available and validated, this additional imaging information has the potential to be valuable as additional ADPKD prognostic markers.

Practice Point 1.4.2.7: Assessment of kidney function as eGFR in relation to age and/or longitudinal eGFR slope data can aid the identification of people with ADPKD and rapidly progressive disease.

Decline in kidney function is an age-related phenomenon in ADPKD. Classically, preserved function for several decades before a steep decline in the decade or so before the onset of kidney failure has been proposed. However, more recent data of plotted trajectories have shown that the rate of decline and associated values at particular ages (age groups) can differ between patient groups (Figures 13 and 14). For instance, a more linear decline from an earlier age is suggested for the more severe MICs (1C–1E) and truncating PKD1 mutations, while the milder groups have the more traditional trajectory. In the systematic analysis for these guidelines, 11 of 17 studies found an association between eGFR and future outcomes (Supplementary Table S2). For instance, in multivariate analysis of 608 people with PKD1 and PKD2, a 10 ml/min per 1.73 m² lower eGFR at baseline resulted in a 55% higher risk of kidney failure at any point during follow-up (follow-up average 16.8 y). Various guidelines have included measurements of kidney function related to age as part of the criteria to identify rapidly progressive people. In the ERA Workgroup for Inherited Kidney Diseases (WGIKD)/The European Rare Kidney Disease Reference Network (ERKNeT) position statement, eGFRs compatible with rapid progression were: any: 18–39 y; <90: 40–44 y; <75: 45–49 y; and <60: 50–55 y. Cut-offs for below average eGFRs or evidence for early decline in the data of Lavu et al. were approximately: <90: 25 y; <80: 35 y; <60: 45 y; and <30: 55 y. However, since many people that will reach kidney failure by age 65 have preserved kidney function for the first few decades of life, using eGFR alone in younger people is not a very accurate way to identify rapid progression.

As expected, the slope of eGFR decline is associated with future functional outcomes and has been suggested in guidelines to be helpful to identify rapidly progressive people. A relatively consistent average decline in eGFR has been described in various cohorts including HALT-PKD Study A (15–49 y at baseline) of -3.5 ml/min per 1.73 m² per y in the standard BP group, approximately -3.9 ml/min per 1.73 m² per y in the HALT-PKD Study B group (18–64 y), -3.7 ml/min per 1.73 m² per y in the TEMPO control group (18–50 y) and -3.61 ml/min per 1.73 m² per y in the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) study (18–65 y). The decline of measured GFR in people with ADPKD in the Modification of Diet in Renal Disease (MDRD) study was -4.4 ml/min per y. Many of these studies were selected for more rapidly progressive people and in the less selected Irazabal et al. 2015 population, the moderate, MIC: 1C group had an average decline of -2.63 ml/min per 1.73 m² per y; -2.63 and -2.43 ml/min per 1.73 m² per y for males and females, respectively. However, the data in Figures 13 and 14 show the level
of decline can change over time and is related to the MIC. The ERA WGIKD/ERKNeT position statement concluded that an eGFR rate of decline of -3 ml/min per 1.73m$^2$ per y was a suggestion of rapidly progressive disease.\textsuperscript{147} This was made with the understanding that eGFR measurements have a high level of sampling variability and so the decline should be documented over a period of $\geq$4 years.

The Work Group considers that the rate of decline of eGFR is a useful measurement to determine kidney disease severity in people with ADPKD, but multiple measurements over a significant period are needed for these data. However, similar information can be obtained from age-adjusted eGFR data of the affected person by comparison to reference data (Figures 13 and 14). These data are of limited use in the youngest adults, although people with the most severe forms of ADPKD may have a decline in eGFR by age 25 years.\textsuperscript{95} Information about eGFR can be particularly helpful when there is a discrepancy between TKV and eGFR data, with a lower eGFR than expected, indicating that further analysis, including genetic testing, may be helpful.

**Practice Point 1.4.2.8: The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score can aid the identification of people with rapidly progressive disease over 35 years of age.**

As highlighted above, the gene causing ADPKD and the variant type for \textit{PKD1} is associated with the severity of kidney disease. Similarly, the affected person’s sex also has an association with kidney disease outcomes, with males on average experiencing earlier kidney failure. Onset of hypertension in ADPKD is on average in the early 30s and being hypertensive before age 35 has been defined as a risk factor for more rapid disease progression. Occurrence of hematuria or urinary tract infections (UTI) have also been associated with lower kidney function.\textsuperscript{94} The PROPKD study\textsuperscript{30} developed an algorithm based on these factors that are associated with poorer outcomes (Figure 14). This simple scheme can be useful to identify people at risk for rapidly progressive disease and can be employed when kidney imaging data are not available. However, it should be noted that genotype data are required, and categories cannot be reliably assigned for people <35 years of age if they are not already hypertensive or have not had a urological event.
Practice Point 1.4.2.9: Urine and serum measured biomarkers are potentially useful to assess prognosis and monitor treatments in ADPKD.

Given the costs and complexities of kidney imaging and genotyping in ADPKD, there have been considerable efforts to develop better prognostic and treatment monitoring urine and serum biomarkers in ADPKD.\textsuperscript{134, 150-154} However, at this stage, most have not outperformed the traditional means of monitoring kidney function, SCr, and cystatin C, and development of improved biomarkers is an area of future research.

One possible promising biomarker is copeptin, a surrogate marker of vasopressin that may be associated with ADPKD pathogenesis. In a study of 79 participants with ADPKD conducted in the Netherlands, the baseline copeptin level in a model including age, gender, and baseline GFR was inversely associated with change in eGFR during 11.2 y of follow-up (p<0.01).\textsuperscript{155}

**Research recommendations**

- Can we identify new genes associated with ADPKD and ADPLD?
- Do germline genetic variants beyond the disease-causing gene influence the severity of kidney disease? And if so, what are they and how can they be identified?
- Do germline genetic variants in the normal copy of the disease-causing gene influence the severity of kidney disease? And if so, what are they and how can we identify them?
- Do somatic variants to the disease-causing gene and beyond influence the severity of kidney disease?
- Does caloric restriction and/or specific diets influence the severity of kidney disease in ADPKD?
- Does smoking influence the severity of kidney disease in ADPKD?
- Does regular exercise influence the severity of kidney disease in ADPKD?
• Does caffeine consumption influence the severity of kidney disease in ADPKD?
• Is AKI a factor that significantly worsens the kidney disease in ADPKD?
• Do comorbidities, such as diabetes, influence the rate of kidney disease progression?
• Is vascular disease an important factor influencing kidney disease progression?
• What is full phenotypic range and kidney disease penetrance for the minor ADPKD genes?
• Can the type of \textit{PKD1} pathogenic variant be better defined to determine the resulting kidney phenotype?
• Can measurement of RBF be better determined and be useful as an early prognostic marker?
• Can better urine and serum biomarkers of ADPKD progression be developed and validated?
• Can a model that includes multiple imaging, genetic, clinical and biomarker inputs better predict disease outcomes in ADPKD?
• Can additional imaging parameters be used to better predict future kidney function?
• Can better predictive urine and serum biomarkers of ADPKD treatment be developed?
CHAPTER 2. KIDNEY MANIFESTATIONS

2.1. Hypertension

High BP is the most common and earliest clinical manifestation of ADPKD. The majority of people are diagnosed with high BP before the age of 30 and early onset high BP is an established clinical risk factor for progression to kidney failure in people with ADPKD. The development of high BP is closely associated with kidney cyst burden or TKV, more so than any other kidney manifestation in ADPKD including hematuria, flank pain, cyst infections, or kidney stones. Given that death in people with ADPKD is most commonly due to cardiovascular causes, continual surveillance of BP levels in people with ADPKD may help improve outcomes.

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 (Figure 15).

Figure 15. Blood pressure management in autosomal dominant polycystic kidney disease (ADPKD). ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; HBPM, home blood pressure monitoring; LVH, left ventricular hypertrophy; RAS, renin-angiotensin system.

Regular BP monitoring will provide early detection of high BP and allow for successful BP target achievement. Dietary and lifestyle modifications may be sufficient for BP control in people with mild high BP and are complementary to pharmacotherapy in established high BP.

The Work Group agrees that the following statements from the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD apply to people with ADPKD.
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 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).

The above measures for BP measurement and monitoring have been recommended for the CKD population but should also be equally valid for people with ADPKD as well. These statements apply to all people and are not specific to people with CKD or ADPKD.

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

Nonpharmacologic management focusing on a diet with low-sodium, high-fluid, high-fiber, and low-carbohydrate in conjunction with a healthy lifestyle is critical in managing high BP in people with ADPKD and should complement pharmacologic therapy (Chapter 7). In the post hoc analyses of the HALT Progression of Polycystic Kidney Disease (HALT-PKD) trials (studies A and B), lower dietary sodium intake measured by 24-hour urinary sodium excretion was associated with more favorable kidney disease outcomes. Specifically, a linear mixed model showed a significant association with the annualized rate of TKV growth in HALT-PKD Study A (0.43% per year for each 18 mmol daily urinary sodium excretion; p<0.001) and a Cox proportional hazards model showed a significant association of the averaged 24-hour urinary sodium excretion with an increased risk to reach 50% of the composite endpoint (eGFR, kidney failure, or death). This recommendation is consistent with the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Dietary sodium restriction in both CKD and general population induces short-term reductions in BP. Thus, dietary sodium restriction (i.e., <2 g (or 90 mmol) per day of sodium, or <5 g per day of salt) may improve BP control when used in concert with antihypertensive agents including renin-angiotensin system (RAS) inhibitors. However, sodium intake should be adjusted in some situations (e.g., hot climate, occupational settings of low fluid intake, runners).

Other lifestyle interventions, including adopting a heart-healthy diet, moderate regular physical activities, weight loss among those who are overweight or obese, and reducing alcohol consumption have been demonstrated in randomized controlled trials (RCTs) to lower BP in the
general population.\textsuperscript{157} Smoking cessation may improve endothelial dysfunction and help to normalize BP in people with ADPKD.\textsuperscript{158} Regular exercise, stress reduction, and maintaining ideal body weight may help to keep BP in the normal range similar to people without ADPKD (Chapter 7). Additionally, increased fluid intake, will inhibit the release of vasopressin during waking hours, and may have an impact on cyst growth and blood pressure levels.\textsuperscript{159, 176, 159, 155, 159}

**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 (ID).

*This recommendation places a relatively high value on the potential of slowing the increase in TKV, lowering left ventricular mass index (LVMI), and reducing urinary albumin excretion, and safety and tolerability of targeting lowering BP. This recommendation places a relatively low value on the lack of change in the slope of eGFR.*

**Key information**

*Balance of benefits and harms*

This recommendation considers the efficacy and safety data from the HALT-PKD Study A, an RCT of 558 people with ADPKD aged 18–49 years with CKD G1–G2 and high BP.\textsuperscript{148} Using a 2-by-2 factorial design, this study tested the efficacy and safety of combined angiotensin-converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB) treatment versus ACEi alone, as well as standard (120/70 to 130/80 mm Hg) versus low (95/60 to 110/75 mm Hg) BP targets on TKV. Other secondary outcomes were also included in this trial (i.e., slope of eGFR decline, LVMI, and albuminuria). BP targets were assessed by HBPM in this trial.

The study found no difference in the treatment effects between the ACEi and ARB combination versus ACEi alone. However, intensive BP control (target <110/75 mm Hg) over an average of 5 years was associated with a slower increase in TKV (5.6% vs. 6.6%; P=0.006), a greater decline in LVMI (-1.17 vs. -0.57 g/m\(^2\)/year; P<0.0010) and a reduced urinary albumin excretion rate (-3.77% per year vs. 2.43% per year; P<0.001), but no significant difference in the slope of eGFR decline (-2.7 vs. -3.1 ml/min/1.73 m\(^2\); P=0.05 not corrected for multiple comparisons). The intensive BP control was found to be safe and tolerable, with side-effects similar to the standard BP group.

It should be noted that there were more people with PKD2 mutations in the low BP versus standard BP group (19.8% vs. 13.1%) which could potentially skew the results in favor of the low BP group since people with PKD2 mutations tend to have milder disease. When high-risk individuals (i.e., those with MIC 1D or 1E classification) were evaluated in HALT-PKD Study A, the impact of randomization to low BP (<110/75 mm Hg) was even greater with a significant impact on the slope of eGFR decline, as well as increase in TKV.
Several other clinical trials also examined the effects of standard versus rigorous BP control on kidney and cardiac outcomes in people with ADPKD <50 years of age with mixed results; they were limited by small sample size (n<100/treatment arm), post hoc subgroup analysis, and inadequate control of confounding factors. Overall, rigorous BP control appeared to be safe. However, none of these studies demonstrated a difference in the slope of eGFR decline between standard versus rigorous BP control, while two studies showed a slower rate of increase in LVMI associated with vigorous BP control.

Certainty of evidence

The overall certainty of evidence was graded as very low primarily due to the sparseness of evidence for the most critical and important outcomes of interest (Supplementary Table S3). The certainty of evidence for most outcomes was also reduced due to methodological limitations of the trials related to completeness of reporting and lack of blinding (although, the largest trial, HALT-PKD, had no serious methodological limitations). There was low certainty of evidence for the critical outcome of CKD progression despite sparseness of data for any given measure due to inconsistency in measures across studies. There was low certainty of evidence for other critical outcomes due to sparseness of data or high imprecision. There was low certainty of evidence for the important outcome of change in LVMI in adults, because the evidence is derived mainly from one trial, HALT-PKD Study A (although this trial was relatively large and methodologically sound), whereas other small studies provided very low levels of evidence. Given low certainty of evidence for only a single critical outcome and a single important outcome (in adults), we concluded that overall, there is very low certainty of evidence (Level D).

Values and preferences

This recommendation places a high value on the safety, tolerability, and potential benefits of intensive BP control in improving both kidney and cardiovascular outcomes. This recommendation places a lower value on the availability and costs of home BP monitors and patient burden for HBPM. While some people will find HBPM challenging and not acceptable, the benefits of this recommendation likely exceed its potential inconvenience, and we believe that many well-informed people with ADPKD would be interested in intensive BP control and HBPM.

Resource use and costs

This recommendation will require extra resources including access to HBPM and time commitment by both the patient and physician to achieve the target BP goal. We recognize that people who are financially disadvantaged may not have access to these resources.

Consideration for implementation

This recommendation holds true for any person aged 18–50 years with CKD G1–G2 and high BP (>130/85 mm Hg) who wishes to pursue an intensive BP control strategy to treat ADPKD. Any person who is interested in this treatment option should be informed about its potential risks and benefits, as well as the advantages for HBPM with its associated costs, training, and time commitment. Regular BP measurements in both the lying and then standing
positions for postural hypotension may minimize the risks of excessive BP control. Regular monitoring is defined as weekly during initial implementation and then monthly after stable BP control has been achieved.

Rationale

The HALT-PKD Study A showed that intensive BP control (<110/75 mm Hg) by RASi as measured by HBPM was associated with a slower rate of increase in TKV, a greater decline in LVMI, and urinary albumin excretion.148 Furthermore, the intensive BP control was safe and tolerable, similar to those in the control group treated to a moderate level of BP control (130/85 mm Hg). Although currently there is no evidence to support intensive BP control in slowing CKD progression in ADPKD, there exists strong evidence that intensive BP control in people with CKD is generally safe and likely to be beneficial for the cardiovascular outcomes. The Work Group judged that most informed people with ADPKD would also value the cardioprotective effects of intensive BP control.

Recommendation 2.1.4: For people with ADPKD ≥50 years of age and/or with more advanced CKD (CKD G3-G5), we suggest a target mean systolic blood pressure (SBP) <120 mm Hg, if tolerated, using standardized office blood pressure BP measurement (2B).

This recommendation places a higher value on one large RCT which showed that targeting a mean SBP to <120 mm Hg (versus <140 mm Hg) in people with CKD without diabetes was associated with reduced cardiovascular events and all-cause mortality. This recommendation places a lower value on the increased risk of mild adverse events in the same trial. This recommendation is weak according to GRADE, based on a lack of high-certainty evidence to evaluate the optimal BP target in late stages of ADPKD.

Key information
Balance of benefits and harms

There is a lack of high-certainty evidence, including RCTs and systematic reviews, to evaluate the optimal BP target in late stages of ADPKD. One large RCT (Systolic Blood Pressure Intervention Trial [SPRINT]) showed that targeting a mean SBP to <120 mm Hg (vs. <140 mm Hg), as measured by standardized office BP, is associated with reduction of cardiovascular events and all-cause mortality, but no difference in kidney outcome in people with CKD without diabetes.162 However, targeting a mean SBP <120 mm Hg was associated with increased risk of adverse events including hypotension, syncope, electrolyte abnormalities, or AKI, but not injurious falls. It is worth noting that people with ADPKD were excluded from the SPRINT trial but were studied in the HALT-PKD B trial which had a BP target of <130/80 mm Hg which was very well-tolerated.149 This recommendation reflects a balance of the potential benefits of achieving the target BP goal and its associated risk of adverse events.
Certainty of evidence

The evidence for the effects of targeting a mean SBP to <120 mm Hg on clinical outcomes such as cardiovascular events and all-cause mortality in people with CKD without diabetes is considered moderate, while the effect on kidney failure is weak.\textsuperscript{157} It should be noted that the mean (SD) age of the participants of the SPRINT trial was 67.9 (9.4) years which is older than most people with ADPKD and CKD G3–G5.

Values and preferences

The Work Group places a high value on reducing the risk of cardiovascular events and all-cause mortality using this BP target, while recognizing that there are potential risks for harms in targeting a mean SBP <120 mm Hg (vs. 140 mm Hg). Thus, the adaptation of an SBP <120 mm Hg is an ideal topic for shared decision-making between individual patients and clinicians.

Resource use and costs

Compared to a more liberal BP target (i.e., SBP <140 mm Hg), there may be increased burden to patients and providers (i.e., increased pill burden, more blood work, and clinic visits). The costs of standardized office BP measurements and additional drugs to achieve target BP goal are modest in view of the benefits. However, the Work Group recognizes that there may be variations in resource availability for people with different socioeconomic backgrounds and between different healthcare systems.

Consideration for implementation

The use of standardized office BP measurement is discussed above and will require additional equipment, clinic space, training, and/or change in culture, habits, or policy. Additionally, the clinician should be aware that the target goal is a mean SBP of ~120 mm Hg for most people, and flexibility needs to be exercised to accommodate people who cannot achieve this target due to adverse side effects.

Rationale

There is a lack of high-certainty evidence to evaluate the optimal BP target in late stages of ADPKD. The SPRINT trial, the only RCT that examined the optimal BP target in people with CKD without diabetes, found that targeting a mean SBP to <120 mm Hg (compared to <140 mm Hg), as measured by standardized office BP, is associated with reduction of cardiovascular events and all-cause mortality, but no difference in kidney outcome.\textsuperscript{162} It should be noted that people with ADPKD were excluded from this trial, that the trial participants are older than most people with ADPKD and CKD G3–G5, and that targeting a mean SBP to <120 mm Hg was associated with increased risk of adverse events including hypotension, syncope, electrolyte abnormalities, or AKI, but not injurious falls. Our recommendation reflects a balance of benefits and harms as well as uncertainty of evidence and is consistent with that from the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease.\textsuperscript{157}
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 \( (IC) \).

This recommendation places a relatively high value on the kidney and cardioprotective effects of RASi in people with CKD. The recommendation is moderate according to GRADE because of limited evidence from RCT in people with ADPKD. However, the Work Group judged that most informed people with ADPKD would value the cardioprotective effects of RASi in CKD and that treatment with RASi in the HALT-PKD Study A was safe and well tolerated.

Key information

Balance of benefits and harms

Multiple RCTs in people with kidney diseases without diabetes have shown that RASi confers a class-specific kidney and cardioprotective effect; however, people with ADPKD are generally underrepresented in these trials. Although activation of systemic and local renin-angiotensin system (RAS) in ADPKD has been proposed to promote cyst growth and CKD progression, definitive RCTs to confirm a class-specific kidney-protective effect of RASi in ADPKD have not been performed. A few comparative studies of RASi versus other antihypertensive agents were limited by small sample size and mixed results. The only large trial of antihypertensive therapy performed in people with ADPKD, the HALT-PKD A and B studies, compared ACEi versus ACEi plus ARB, because the steering committee and funding agencies considered the preponderance of evidence supporting RASi as the most beneficial treatment for people with ADPKD. Therefore, the recommendation to use RASi as first-line antihypertensive drugs in ADPKD places a relatively high value on the cardioprotective benefits of RASi in CKD and on the demonstrated safety and tolerability of these agents.

Certainty of evidence

The overall certainty of evidence regarding the comparison of RASi versus other antihypertensives was graded as low primarily due to sparseness of evidence for any given drug comparison and a lack of evidence for most critical and important outcomes of interest (Supplementary Table S4). The studies each had some methodological concerns, mostly related to unclear reporting of study design methods which led to a downgrading of the certainty of evidence. Under the assumption that the various RASi had similar effects to each other and that non-RASi (beta blockers and calcium channel blockers) had similar effects to each other, we found moderate certainty of evidence related to the critical outcome of effect on BP control, with no major concerns other than methodological quality. We found some inconsistency across studies related to the effect of RASi on the critical outcome CKD progression, resulting in a low certainty of evidence. No studies addressed other critical outcomes. Based on a single, small study, there was very low certainty of evidence for the important outcome of LVMI. No studies addressed other important outcomes. With moderate certainty of evidence only for one critical outcome (BP) and low certainty of evidence for another critical outcome (CKD progression), but
no or very low certainty evidence for other outcomes, we concluded that overall, there is low certainty of evidence (Level C).

Values and preferences

The Work Group places a high value on the kidney and cardioprotective effects of ACEi and ARB for people with ADPKD. Based on these benefits, RASi are the preferable first-line agents for treating high BP in people with ADPKD. In the presence of the best certainty data possible in this population, the Work Group judged that most informed people with ADPKD would value the cardioprotective effects of RASi given that the HALT-PKD Study A demonstrated that these treatments are safe and well tolerated.

Resource use and costs

The risks, benefits, resource use, and costs of RASi should be discussed with the patient. RASi are currently widely available worldwide with relatively low cost associated with their use.

Consideration for implementation

RASi should be administered using the highest approved dose that is tolerated to achieve the benefits described in RCTs using these doses. Changes in BP, SCr, and serum potassium should be checked within 2–4 weeks of initiation or dose increase of a RASi. Hyperkalemia associated with the use of RASi can often be managed by dietary potassium restriction, discontinuation of other hyperkalemic drugs, or addition of a potassium-wasting diuretic or oral potassium binders. RASi therapy should be continued unless SCr rises by >30% within 4 weeks following initiation or a dose increase. However, dose reduction or discontinuation of a RASi should be considered in the setting of symptomatic hypotension or uncontrolled hyperkalemia. RASi do not need to be discontinued in CKD G4–G5 in the absence of hypotension or uncontrollable hyperkalemia.

Rationale

High BP is an early clinical manifestation of ADPKD occurring in >60% of people before 30 years of age when kidney function is usually still normal or near normal (eGFR >80 ml/min per 1.73 m²). There is a significant correlation between the presence of high BP and cyst burden or TKV. High BP develops in ADPKD in part due to intrarenal ischemia and activation of the intrarenal RAS due to cyst expansion and pericystic compression of intrarenal blood vessels, similar to the cause of high BP in people with bilateral renal artery stenosis. Thus, there is a strong biological rationale for the use of RASi in people with ADPKD. However, it is unclear whether RASi confers a class-specific effect in improving kidney outcomes in ADPKD beyond that of BP control. Direct comparative studies between RASi versus other class of antihypertensive agents were few and showed mixed results; most were limited by multiple methodological concerns including small sample size and lack of control for biases and confounding. Nevertheless, RASi was found to be safe and well-tolerated in the HALT-PKD A and B studies and conferred a cardioprotective effect in RCTs of people with CKD, making it a reasonable first-line agent for high BP treatment in ADPKD.
We agree with the following statement from the *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD* and feel this recommendation should apply to people with ADPKD.\(^{157}\)

**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 (*IB*).

There is growing evidence in people with CKD with or without diabetes that dual RASi blockade with an ACEi, and ARB does not lead to long-term kidney or cardiovascular benefits despite a reduction of proteinuria in the short term. It also leads to an increased risk of harm from hyperkalemia and AKI. The *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD* issued a strong recommendation against the use of dual RASi therapy based on review of multiple RCTs of people with CKD.\(^{157}\) However, it should be noted that people with ADPKD were generally not well-represented in most of these RCTs. On the other hand, the HALT-PKD studies (A and B) have failed to demonstrate a therapeutic benefit of the combined ACEi and ARB treatment versus ACEi alone in both early and late stages of ADPKD.\(^{148, 149}\) Thus, dual RASi therapy should not be used in ADPKD.

**Practice Point 2.1.4:** Resistant high BP requiring ≥3 drugs should be investigated for causes of hypertension other than ADPKD.

Observational cohort studies and RCTs have shown that BP reduction in people with ADPKD is reasonably easy to achieve with a small number of antihypertensive agents. The HALT-PKD trial demonstrated that on average 2 medications were needed to reach a BP goal of 110/75 mm Hg. Therefore, if an individual demonstrates BP that is difficult to control with ≥3 drugs that are optimally dosed, it is reasonable to consider evaluation for secondary causes of hypertension other than ADPKD. Medication compliance and dietary sodium discretion should be confirmed. In addition, people with symptoms or clinical findings consistent with secondary causes of hypertension should also be evaluated for secondary causes of hypertension.

**Practice Point 2.1.5:** Echocardiogram and urinalysis should be performed to assess hypertensive end-organ damage.

End-organ damage related to hypertension in ADPKD can be detected by measuring the LVMI to identify left ventricular hypertrophy (LVH). Adults with ADPKD and high BP should undergo an echocardiogram to assess the presence of LVH and valvular heart disease (Chapter 3). If LVH is present, repeating the echocardiogram annually for follow-up may be reasonable.

Proteinuria is uncommon in ADPKD occurring in less than 20% of adults and typically low grade (<0.5 g/day). Serial urinary protein or albumin measurements at baseline and annually
thereafter may help to assess BP control in people with ADPKD and high BP. However, high-grade (i.e., >2–3 g/day) proteinuria should alert the likelihood of a second coexisting kidney disease such as glomerulonephritis.

Research recommendations
• Studies are needed to determine whether the BP target of 110/75 mm Hg is beneficial in older adults with ADPKD, high BP, and reduced kidney function similar to those who participated in the HALT-PKD Study B where BP goals were maintained at 130/85 mm Hg.
• Studies are needed to identify predictive plasma and urinary biomarkers for beneficial kidney outcomes in the setting of rigorous BP control in ADPKD.
• Studies are needed to determine whether other classes of antihypertensive agents, including sodium glucose cotransporter-2 inhibitors (SGLT2i) impact change in TKV, eGFR, urinary albumin excretion, or LVH in people with ADPKD.

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).

Chronic kidney pain in ADPKD is defined as flank, abdominal, or back pain that lasts longer than 3 months. It can be caused by renal capsule distention or traction on the renal pedicle secondary to cyst expansion, or occur following an episode of acute pain (such as originated by cyst infection or cyst hemorrhage) that results in nociceptive stimulation. It can be aggravated by mechanical back pain due to abnormal posture from cystic kidney enlargement.

The severity of chronic pain shows little correlation with kidney volume, so people with mild or moderate cysts may occasionally develop disabling pain. A previous study (HALT-PKD studies A and B) showed no association between pain and TKV in people with early disease (CKD G1–G2), except in individuals with large kidneys (htTKV >1000 ml/m), but pain was more severe in people with late (CKD G3b–G4) disease.

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

Identification and resolution of likely causes of chronic kidney or liver pain in ADPKD is critical (Chapter 5). People with refractory chronic kidney or liver pain should be screened for depression. When refractory and/or complex, it is best managed by a multidisciplinary team, whose potential therapeutic interventions are outlined in the pain management infographic below (Figure 16).
Figure 16. Shared decision-making in management of chronic kidney pain in autosomal dominant polycystic kidney disease (ADPKD). ADPKD, autosomal dominant polycystic kidney disease; PLD, polycystic liver disease; TENS, Transcutaneous electrical nerve stimulation

Practice Point 2.2.3: Shared decision-making between the physician and the patient or caregiver should guide the decision on pain management strategies in ADPKD.

Shared decision-making between the physician and the patient or caregiver should be applied to the pain management approaches whenever possible, particularly to the more complex decisions and interventions (Figure 16). This process is expected to reduce patient’s anxiety, increase patient’s cooperation, and respect patient’s personal choices and views. In some cases, reassurance alone can help alleviate perceptions of pain and anxiety.

Practice Point 2.2.4: Nonpharmacological, noninvasive interventions should generally be considered as the initial treatment of chronic kidney pain in ADPKD.
The efficacy and selection criteria of most nonpharmacological interventions to treat chronic kidney pain in ADPKD have not been established. Although physical therapy interventions (e.g., heat pads, ice massage, light exercise, and/or whirlpool) and improvement in body posture and mechanics (e.g., Alexander technique\textsuperscript{178}) have not been systematically evaluated, there may be benefits in some people with chronic back pain. In people with pain due to renal pedicle traction associated with enlarged kidneys, a support garment may help pain control.\textsuperscript{174} Acupuncture and transcutaneous electrical nerve stimulation (TENS) may also provide relief;\textsuperscript{174} however, these options should be reserved to people with pain not responsive to nonopioid pharmacological interventions.

**Practice Point 2.2.5:** Stepwise pharmacological treatment for chronic kidney pain in people with ADPKD should be implemented when physical therapy does not adequately relieve pain.

Acetaminophen is the first-line drug for chronic pain control. Nonsteroidal anti-inflammatory drugs (NSAIDs) are discouraged for chronic pain but may be used short-term for acute pain in people with stable kidney function.\textsuperscript{179} Tricyclic antidepressants and gabapentin may also be useful as analgesic adjuvants, despite the lack of RCTs in ADPKD.\textsuperscript{180} Experience with pregabalin in ADPKD is still limited. Tramadol can be used either as a next-line agent or as adjunctive therapy in people with pain not appropriately controlled with the previous drugs. Clonidine is an option when acetaminophen and tramadol are not effective or contraindicated.

Opioids or minimally invasive therapies are options for people with no response to nonopioids or noninvasive therapies (Figure 16). Opioid use should be limited and employed only after failure or inadequacy of all previous approaches. If high-dose opioids are required to appropriately relieve pain, they should be used as a short-term plan, avoiding long-term treatment. When employed, opioids may be more effective when administered with other analgesics. In people with reduced kidney function, opioid dosing should be adjusted, and meperidine should be avoided.

Nonpharmacologic and nonopioid pharmacologic therapy should be maximized to control chronic kidney pain in people with opioid dependency. Buprenorphine may be used for chronic pain control in some of these cases; however, no systematic study addressing this issue has been reported to date. In people with chronic kidney pain and no responsiveness to nonpharmacologic and nonopioid pharmacologic anti-pain modalities, invasive interventions should be considered, if appropriate, to avoid opioid dependency.

**Practice Point 2.2.6:** The sequential approach and best choice of invasive intervention for chronic kidney pain in ADPKD depends on cyst characteristics and on the local expertise of the surgeon/interventional radiologist which may vary between centers and countries. Referral to a center of expertise should be made whenever possible.
A sequential approach to the choices of minimally invasive to invasive intervention for chronic kidney pain in ADPKD is proposed in Figure 16. The proposed sequence and choices of procedures, however, assumes the availability of all required interventional expertise. Since such expertise is not universally available, such a sequential approach can vary widely between centers and countries. Thus, local expertise of surgeons and interventional radiologists must be taken into account to guide the best choice of invasive therapy.

**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 center.

Minimally-invasive interventions are options to treat chronic kidney pain in people who do not respond to noninvasive therapies and whose pain can be attributed to a single or multiple dominant cysts. Percutaneous cyst aspiration coupled with injection of a sclerosant to ablate the cystic lining (i.e., sclerotherapy) or laparoscopic cyst fenestration/decortication may lead to long-lasting pain control. Foam sclerotherapy or laparoscopic cyst fenestration are usually employed in people with large (>5 cm) accessible kidney cysts that cause significant “mass effect” symptoms (e.g., abdominal pain and distention, early satiety, heartburn due to acid reflux). The adopted choice is much dependent on the available expertise.

**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.

Diagnostic temporary block of the celiac plexus has been used to assess its effectiveness to provide pain control. An invasive procedure protocol for chronic refractory pain in people with ADPKD showed that most people experienced significant pain relief in response to diagnostic or more definite celiac plexus block. Renal denervation was performed in 5 people with no response to the diagnostic celiac plexus block, resulting in a borderline significant change in pain. Overall, a marked majority of the 44 people included in the study had a sustained improvement in pain intensity after a median follow-up of 12 months. Another small study (n=11) suggests that percutaneous catheter-based renal denervation reduces pain complaints and the use of analgesics in people with ADPKD.

**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.

While spinal cord stimulation may lead to marked pain control in specific cases of moderate-to-severe refractory mechanical or visceral pain, it must be noted that, depending on the implanted device, it may preclude the performance of MRI studies. This concern is mainly based on the potential heating of the generator and/or tip of the lead and the electrodes.
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.

Nephrectomy can be considered when everything else has failed to alleviate pain, particularly in the setting of kidney failure.\(^{171}\) Laparoscopic nephrectomy is usually preferred over open surgery, since it is associated with smaller blood loss, faster recovery, and less pain. Open nephrectomy may be considered in people with extremely large kidneys, although some authors consider that hand-assisted laparoscopic nephrectomy can be considered a technique of choice for massive kidneys.\(^{187}\)

A multidisciplinary stepwise protocol including analgesics, cyst sclerotherapy or fenestration, nerve blocks, and nephrectomy (usually in people on dialysis) in people with ADPKD complaining of refractory pain was effective in reducing pain in most people.\(^{176}\)

**Research recommendations**

- Studies are needed to compare the cost-effectiveness of different nonpharmacological, noninvasive interventions as initial treatment for chronic kidney pain in people with ADPKD.
- Studies are needed to compare the cost-effectiveness of different minimally invasive interventions in people with no response to noninvasive, antipain therapies and with no clear indication for a given procedure.

2.3. Nephrolithiasis

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

Review of prior history and related records of kidney stones should be routinely included in all people with ADPKD. A significant number of people with ADPKD develop one or more kidney stones during their clinical course.\(^{188}\) In a recent meta-analysis, the prevalence of kidney stones ranged from 3%–59% in people with ADPKD, and this was higher compared to their unaffected family members (risk ratio [RR]: 1.8; 95% CI: 1.3–2.6).\(^{189}\) Both anatomic distortions of the kidneys and metabolic factors may play a role in increased stone formation for people with ADPKD. In the general population, calcium oxalate and calcium phosphate stones account for >80% of the cases, while uric acid stones account for <10% of the cases.\(^{188}\) However, the frequency of uric acid stones may be increased in people with ADPKD compared to the general population.\(^{188}\) CT scan and ultrasound do not differentiate uric acid from calcium stones. Dual energy CT is needed to differentiate these stones, but it may not be widely available.

Practice Point 2.3.2: Screening for kidney stones in people with ADPKD who have no history of kidney stones should be individualized.
There is currently no uniform consensus on screening for kidney stones in people with ADPKD. Many centers routinely screen their patients for kidney stones with the same ultrasound used for first diagnosis of ADPKD, however, ultrasound is not sensitive. When resources are available, some centers use a low-dose, noncontrasted CT scan for screening which can provide accurate information on the size and number of existing kidney stones for treatment planning.\textsuperscript{188}

**Practice Point 2.3.3:** People with ADPKD and 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 available.

Potential lithogenic risk factors for kidney stones (e.g., low urine output, hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia, and anatomic abnormalities due to cystic kidney enlargement) should be assessed in people with ADPKD and symptomatic kidney stones.\textsuperscript{188, 190-192} Most people with symptomatic kidney stones would already have at least one kidney imaging study (typically, a low-dose noncontrast CT) documenting the number, size, and location of their kidney stones. Two 24-hour urine collections for volume, creatinine, sodium, potassium, calcium, magnesium, oxalate, citrate, and uric acid and a spot urine for urinalysis and pH should be performed to identify any modifiable risk factors. For follow-up, urinary studies should be repeated in one year, and periodically thereafter. Additional follow-up kidney imaging should be individualized. Whenever possible, chemical analysis of kidney stone(s) that have been passed or retrieved surgically should be performed.

The Work Group agrees that the following statements from the *Canadian Urological Association Guideline: Evaluation and medical management of kidney stones* for the general population apply to people with ADPKD.\textsuperscript{193} While the Work Group agrees with the statements below, this is not a formal endorsement of the Canadian Urological Association guideline. Please refer to local guidelines for your region or setting, where available.

<table>
<thead>
<tr>
<th>Recommendations from the <em>Canadian Urological Association Guideline: Evaluation and medical management of kidney stones</em></th>
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<tbody>
<tr>
<td><strong>Recommendation 2.3.1:</strong> All stone formers should be counselled to achieve a daily urine output of 2.5 l (2B).</td>
</tr>
<tr>
<td><strong>Recommendation 2.3.2:</strong> Stone disease highly correlates with obesity, diabetes, and metabolic syndrome; patients should be counselled that proper management of these conditions may reduce their future stone risk (2D).</td>
</tr>
<tr>
<td><strong>Recommendation 2.3.3:</strong> When possible, specific dietary assessments and recommendations should be made with the involvement of a registered dietitian (3C).</td>
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Adequate water and fluid intake are essential to achieve a urine output of at least 2.5 liter/day which has been shown to lower the risk of kidney stones by 60%–80% in the general population.\textsuperscript{194-197} Based on preclinical studies of ADPKD, high water intake may also slow kidney cyst growth by suppressing cyclic adenosine monophosphate (c-AMP), although its clinical effectiveness has not yet been proven.\textsuperscript{198, 199} A healthy diet rich in fiber, fruits, and vegetables, but not in sodium and animal protein, similar to that recommended for hypertension, obesity, diabetes, and metabolic syndrome may also be appropriate for people with kidney stones. Additionally, the results of the urinary lithogenic marker studies and stone chemical analyses should be used to guide the treatment.

Assessment with a registered dietitian is strongly suggested where there is a history of compromised nutritional status, complex medical situations, or people who need assistance implementing dietary recommendations. Evidence suggests that people who received specific dietary recommendations based on a comprehensive evaluation had fewer stone recurrences over 3 years than those who only received general dietary advice.\textsuperscript{200}

**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.

The presence of large kidney cysts may make extracorporeal shock wave lithotripsy or percutaneous nephrostomy more difficult to perform. In general, depending on the level of the ureteric obstruction (proximal, mid-, or distal) and the size of the stone (> or <10 mm), extracorporeal shock wave lithotripsy or ureteroscopy may be the preferred first-line treatment, while percutaneous nephrostomy is generally considered as a second-line intervention. The results of these interventions to treat obstructing stones are highly variable between centers and procedure types.\textsuperscript{201}

**Research recommendations**

- A cost-effectiveness analysis of asymptomatic kidney stone screening strategies is needed for people with ADPKD (e.g., using the same ultrasound for first diagnosis of ADPKD vs. a dedicated, low-dose, noncontrasted CT scan). This also requires more accurate estimates of the prevalence of symptomatic and asymptomatic kidney stones in ADPKD.

- The relative contributions of anatomic and metabolic factors for stone formation in ADPKD are unclear. A better understanding of pathogenesis is required for effective pharmacologic prevention and treatment strategies.
2.4. Gout

There is currently no evidence that the prevalence of gout is greater in ADPKD. However, gout is prevalent in the general population and more common in people with CKD; therefore, gout management is a concern for people with ADPKD.202

The Work Group agrees that the following statements from the 2020 American College of Rheumatology Guideline for the Management of Gout for the general population apply to people with ADPKD.203 While the Work Group agrees with the statements below, this is not a formal endorsement of the American College of Rheumatology guideline. Please refer to local guidelines for your region or setting, where available.

Recommendations from the 2020 American College of Rheumatology Guideline for the Management of Gout:

Recommendation 2.4.1: For patients experiencing their first flare, we conditionally recommend against initiating urate-lowering therapy (ULT) over no ULT, with the following exceptions.

Recommendation 2.4.2: For patients experiencing their first flare and CKD stage ≥3, serum urate (SU) >9 mg/dl, or urolithiasis, we conditionally recommend initiating ULT.

Recommendation 2.4.3: For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl with no prior gout flares or subcutaneous tophi), we conditionally recommend against initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid) over initiation of pharmacologic ULT.

Recommendation 2.4.4: For patients starting any ULT, we strongly recommend allopurinol over all other ULT as the preferred first-line agent for all patients, including those with CKD stage ≥3.

Recommendation 2.4.5: For allopurinol and febuxostat, we strongly recommend starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., ≤100 mg/day [and lower in patients with CKD] for allopurinol or ≤40 mg/day for febuxostat).

Recommendation 2.4.6: We conditionally recommend testing HLA-B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American patients, who have a higher prevalence of HLA-B*5801.

The above statements for management of gout have been recommended for the general population but should be equally valid for people with ADPKD as well. These statements apply to all people and are not specific to people with CKD or ADPKD.
Practice Point 2.4.1: People with ADPKD should not be treated for asymptomatic hyperuricemia.\textsuperscript{203}

The Work Group agrees with the \textit{2020 American College of Rheumatology Guideline for the Management of Gout}.\textsuperscript{203} There is currently no evidence that ADPKD is associated with hyperuricemia or that medical treatment of hyperuricemia slows the progression of ADPKD.\textsuperscript{204}

However, as for the general population, if a person presents with a diagnosis of asymptomatic hyperuricemia, it is appropriate to counsel on healthy dietary changes, including limiting intake of alcohol, high-purine foods and high-fructose corn syrup, and weight loss to prevent gout and improve general health.\textsuperscript{203} Risk factors for hyperuricemia in people with ADPKD are similar to those in the general population. These include male sex, older age, higher BMI, and most importantly decreased kidney function.\textsuperscript{204} Use of diuretics was not associated with hyperuricemia in the HALT-PKD study.\textsuperscript{204}

Practice Point 2.4.2: People with ADPKD and gout should be evaluated and treated accounting for their level of kidney function.\textsuperscript{203, 205}

The Work Group agrees with the \textit{2020 American College of Rheumatology Guideline for the Management of Gout} which recommends prescribing urate-lowering medications for people with gout and subcutaneous tophi, radiological evidence of joint destruction attributable to gout, or $\geq 2$ gout attacks per year.\textsuperscript{203, 204} Allopurinol is recommended as the preferred first-line agent, including people with moderate-to-severe CKD (CKD G4–G5). However, these people with moderate-to-severe CKD require initiation with a low dose of allopurinol (50 mg/day), close monitoring for adverse effects, and slow up-titration of the allopurinol dose (by 50–100 mg/d every 4 weeks).\textsuperscript{205} Providing anti-inflammatory prophylaxis for 3–6 months (e.g., colchicine 0.6 mg/day for CKD G1–G3, 0.3 mg/day for CKD G4, and 0.3 mg twice a week for CKD G5, with close monitoring for side effects) is recommended when starting urate-lowering medications.\textsuperscript{203, 205}

Because people of Southeast Asian and African descent carry the HLA-B*5801 allele (linked to allopurinol hypersensitivity syndrome) more often than White or Hispanic people, testing for this allele is conditionally recommended in these people before starting allopurinol. The American College of Rheumatology guideline also recommends treating all people to target (i.e., achieving a serum uric acid level of $< 6$ mg/dl [$< 0.36$ mmol/l]). Febuxostat can be used in people who are intolerant of allopurinol, starting at 40 mg/d and uptitrating to 80 mg, if needed. However, febuxostat may be associated with a slightly higher risk of cardiovascular events.\textsuperscript{203, 205}

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).
Early onset hyperuricemia and gout are not typical features of ADPKD but are commonly seen in people with uromodulin (UMOD) or HNF1β mutations, which are causes of ADTKD.\textsuperscript{16} Thirty to 40\% of people with UMOD mutations have kidney cysts, usually distributed in the kidney medulla, which can be misdiagnosed as ADPKD, especially in the younger people.\textsuperscript{81}

2.5. Hematuria

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

Gross hematuria is a common clinical finding that is often distressing to people with ADPKD.\textsuperscript{206, 207, 220, 206, 200, 201} A precipitating event, such as physical trauma to the abdomen or strenuous activity, can be occasionally identified; however, most episodes occur spontaneously. Spontaneous hematuria is more likely among people with larger kidneys, hypertension, and advanced stages of CKD.\textsuperscript{183} Early onset (i.e., <30 years of age) gross hematuria is associated with more rapid progression of kidney disease in people with ADPKD.\textsuperscript{208}

Cyst hemorrhage and rupture into the collecting system is thought to be the cause of hematuria in people with ADPKD; however, although cyst hemorrhage is common, the typical presentation is pain, rather than hematuria, since many cysts do not communicate with the collecting system.\textsuperscript{206} The differential diagnosis should include cystitis, passage of a kidney stone, and immunoglobulin A (IgA) nephropathy. Gross hematuria due to cyst rupture generally resolves within 2–7 days with conservative therapy that consists of bedrest, hydration, and analgesics that exclude NSAID, except for short-term use (<1 week) in people with preserved kidney function. Antibiotics are not indicated unless gross hematuria is associated with culture-proven infection. Occasionally, bleeding can persist for several weeks. With unusual and severe bleeding, percutaneous arterial embolization or even nephrectomy may become necessary.\textsuperscript{209} Prolonged or recurrent hematuria should raise the possibility of an underlying kidney or urological problem other than ADPKD, such as IgA nephropathy, renal cell carcinoma (RCC), or bladder or prostate cancer.

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

If hematuria is associated with pain, fever or other systemic symptoms, the severity of these symptoms will lead the person to seek medical attention. If hematuria is painless, it often resolves spontaneously within a day or two. In this case immediate medical attention may not be necessary, but the person should increase fluid intake and monitor for any additional symptoms.

Gross hematuria can occur even in children with ADPKD, sometimes after a sports event, and can lead to the diagnosis of ADPKD. This does not mean that the child is predestined to early kidney failure or should not participate in sports. However, should hematuria repeatedly
occur in a child it may be prudent to avoid contact sports in which blunt trauma to the kidney is possible.

2.6. Urinary tract infections

The Work Group agrees that the following statements from the American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) for the general population apply to people with ADPKD. While the Work Group agrees with the statements below, this is not a formal endorsement of the AUA/CUA/SUFU guideline. Please refer to local guidelines for your region or setting, where available.

**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).

Asymptomatic pyuria is relatively common in ADPKD and does not necessarily indicate a UTI. Asymptomatic pyuria and asymptomatic bacteriuria should not be treated with antibiotics (except during pregnancy) which is the same recommendation as for the general population. For documented bacterial cystitis antibiotics such as nitrofurantoin, trimethoprim-sulfamethoxazole, or fosfomycin can be used as first-line therapy, depending on local antibiogram. However, nitrofurantoin is not indicated in people with decreased kidney function (CKD G3–G5) due to concerns of decreased efficacy and increased toxicity (particularly with CKD G4–G5) and should be avoided in older people (>65 years). TMP-SMX dosing also needs to be adjusted to the level of kidney function. Decrease the dose by 50% in CKD G4 and by
50%–75% in CKD G5, with close monitoring, as acute interstitial nephritis is a potential complication of treatment with TMP-SMX.

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

Recurrent UTIs (i.e., 2 separate culture-proven episodes within 6 months or 3 episodes within 1 year) may be due to an inadequately treated infection (bacterial relapse) or reinfection and should be investigated for a possible underlying predisposition such as an infected stone, partially treated infected kidney cyst, or urethral diverticulum. Bacterial relapses can be due to an infected cyst or kidney stone and a prolonged course of antibiotics, and additional interventions such as cyst drainage or surgical stone removal may be required. Frequent bacterial reinfections can be due to local factors facilitating bacterial adhesion to urothelial cells, bacterial colonization, or bladder dysfunction and may require studies of bladder function and chronic antibacterial prophylaxis.

**Practice Point 2.6.2: Before antibiotics are started for UTI, especially for upper UTI and/or suspected kidney cyst infection, a urine culture should be conducted.**

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

The clinical presentation of UTI may overlap with cyst hemorrhage or kidney stone. The diagnosis of each of these conditions requires a careful history, physical examination, and laboratory testing including complete blood counts, C-reactive protein (CRP), blood and urine cultures, urinalysis, and abdominal imaging. The presence of fever, abdominal or flank pain, elevated white blood cell counts, and CRP in a person with ADPKD would strongly suggest a cyst infection or pyelonephritis. On the other hand, gross hematuria without fever can occur with cyst hemorrhage or kidney stone which should not be treated with antibiotics in the absence of proven infection.

**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 (Figure 17).**

The presence of kidney point tenderness, pyuria, or positive urine and/or blood culture increases the possibility of kidney cyst infection. The demonstration of a new complex kidney cyst by contrast CT or MRI, although nonspecific (i.e., unable to determine blood vs. pus within the cyst), provides a potential means for localizing the infection; aspiration should be considered for diagnostic confirmation. The presence of certain intra- or pericystic findings (e.g., gas, pericystic inflammatory changes, contrast enhancement, or thickening) by contrast CT or MRI, a positive indium-111 or positron emission tomography with 18F-2-deoxy-2-fluoro-glucose integrated with computed tomography (18F-FDG PET-CT) may provide additional certainty and
localization of the infected cyst(s). The algorithm below is derived from an international multispecialty survey of experts in polycystic kidney and liver disease (Figure 17).\textsuperscript{212}

![Diagnostic algorithm for infected kidney cyst](image)

**Figure 17. Diagnostic algorithm for infected kidney cyst.** CT, computed tomography; \textsuperscript{18}FDG PET-CT, positron emission tomography with \textsuperscript{18}F-2-deoxy-2-fluoro-glucose integrated with computed tomography; Ga67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga et al.\textsuperscript{212}

**Recommendation 2.6:** 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 ADPKD, if possible.

This recommendation places a high value on the potential seriousness of upper UTI in people with ADPKD, the difficulty in achieving sufficient antibiotic levels inside the infected cyst, and the difficulty in establishing a firm clinical diagnosis in many cases. The empirical clinical practice of treating infected kidney cyst(s) with 4–6 weeks of systemic antibiotic was designed to ensure the cyst infection is adequately addressed. This recommendation places a low value on the costs and side effects of this approach. Overall, this is a weak recommendation that is widely accepted by the clinical community.
**Key information**

**Balance of benefits and harms**

Upper UTIs in people with ADPKD have potentially serious implications. Compared to pyelonephritis, infected kidney cysts are thought to require longer duration of antibiotic treatment due to poor penetration into cyst fluid by most antibiotics (except those with lipophilic properties). Additionally, it may be difficult to establish a firm clinical diagnosis of kidney cyst infection. Thus, 4–6 weeks of empirical treatment with a lipophilic antibiotic that covers common urinary pathogens is generally recommended for people with probable or definitive cyst infection. However, prolonged antibiotic treatment may increase the risks of side effects such as *Clostridium difficile* (*C. diff*) colitis and subsequent antibiotic resistance.

**Certainty of evidence**

There are no systematic reviews or comparative studies to evaluate the optimal duration of antibiotic treatment for people with ADPKD and kidney cyst infection. The current recommendation is based on expert opinion with very low certainty of evidence (Level D).

**Values and preferences**

This recommendation places a high value on the seriousness of the kidney cyst infection and the need for adequate treatment. The Work Group recognizes that some people, especially those with recurrent cyst infection and/or serious treatment associated side effects, may find 6 weeks of antibiotic challenging or unacceptable. In this situation, shared decision-making between the patient and the clinician, preferably with the input of an infectious disease specialist, is essential.

**Resource use and costs**

The costs of oral antibiotics (e.g., fluoroquinolone or trimethoprim-sulfamethoxazole) used for infected cyst infection is modest. However, other antibiotics that require intravenous administration may be prescribed in the occasional person with infected cyst due to drug allergy or antibiotic resistance. In this case, home antibiotic treatment may or may not be readily available, depending on the healthcare system.

**Consideration for implementation**

Kidney cyst infection is treated with oral antibiotics, unless a person is septic or actively vomiting, so implementation is usually not an issue. However, in the occasional person in whom i.v. antibiotic treatment is required, additional resources (i.e., home nursing visit for i.v. antibiotic program) will be needed.

**Rationale**

For kidney cyst infection, 4–6 weeks of a lipid-soluble agent such as a fluoroquinolone or trimethoprim-sulfamethoxazole, which penetrates the cyst wall better than the other non-lipid soluble antibiotics, is suggested. Aside from the usual side effects of fluoroquinolones, a black box warning has been issued by the U.S. Food and Drug Administration (FDA) that prolonged
use of this class of antibiotics may be associated with increased risks of arterial and aortic dissection and aneurysm based on clinical and experimental studies.213, 214

It is not unusual for pyelonephritis to lead to a cyst infection. Given that it is difficult to differentiate between the two diagnoses and that both may be present simultaneously, a conservative approach would be to treat upper UTI for 4–6 weeks unless there is a clear indication that it is not a cyst infection. All people with ADPKD and upper UTI should be monitored to evaluate their clinical response to antibiotic treatment. Occasionally, drainage of a putatively infected cyst may be needed in the absence of clinical improvement. In rare instances of frequently relapsing cyst infections despite prolonged antibiotic courses and no large cyst to be drained, chronic suppressive treatment with rotating antibiotics may reduce the emergence of antibiotic resistance. This should be overseen by an infectious disease expert.

**Research recommendations**

- Studies are needed to determine the spectrum of bacteria and their antibiotic resistance patterns of cystitis and upper UTI in ADPKD by geographical region and country.
- Studies are needed to determine whether the duration of antibiotic therapy in upper UTI can be shortened. Prolonged antibiotic therapy predisposes to C. diff and fungal infections and often causes diarrhea and other complications.
- Studies are needed to determine clinical efficacy of alternative antibiotic regimens given the potential adverse effects of fluoroquinolones and increasing antibiotic resistance.

### 2.7. Renal cell carcinoma

**Practice Point 2.7.1:** In the current state of knowledge, there is no clear association between ADPKD and an increased risk of renal cell carcinoma (RCC).

RCC is an infrequent complication documented in people with ADPKD. Conflicting data exist on the prevalence of RCC in people with ADPKD. A large Taiwanese national cohort study of people with (n=4346) and without ADPKD (n=4346) showed an increased kidney cancer risk (adjusted HR: 2.45; 95% CI: 1.2–4.65) in ADPKD.215 By contrast, 2 smaller registry studies of people with kidney failure or kidney transplant did not show an increased risk of RCC in ADPKD compared to other chronic kidney diseases.216

**Practice Point 2.7.2:** Clinicians should be aware of atypical presentation of RCC in ADPKD.

RCC in people with ADPKD, compared to the general population, frequently present with fever (32% vs. 7%), are often bilateral (12% vs. 1%–5%), multicentric (28% vs 6%), and display sarcomatoid features (33% vs. 1%–5%).217 Clinical findings such as hematuria, flank mass, and complex cystic kidney lesions, which are common in people with ADPKD, may confound the diagnosis of RCC. However, the presence of systemic signs or symptoms (fever, fatigue, loss of appetite, weight loss) in the absence of infection or obvious explanation, or
documentation of a rapidly growing complex cystic kidney lesion should raise the suspicion of RCC.\textsuperscript{217} Contrast CT or MRI are often able to distinguish malignancy from complex cysts due to hemorrhage; percutaneous aspiration, and cytologic examination on suspicious lesions may help to establish the diagnosis.

**Research recommendations**

- Studies are needed to determine if the RCC prevalence is increased in people with ADPKD not receiving dialysis versus the general population, adjusting for comorbidities such as the percentage of people with CKD.
- Studies are needed to determine if the RCC prevalence is increased in people receiving dialysis and/or kidney transplants with and without ADPKD, adjusting for comorbidities.
- Studies are needed to determine whether pre-transplant screening for RCC improves outcomes for people with ADPKD.
3.1. CKD management and progression
Practice Point 3.1.1: In general, management of CKD in ADPKD is similar to that in other kidney diseases.

Management of CKD has been reviewed extensively in prior KDIGO guidelines. People with ADPKD should be treated using the same recommended management guidance as for those with CKD unless otherwise specified in this chapter.

A set of general measures relevant for CKD management in people with ADPKD are discussed in specific chapters of this guideline or below, as indicated in Figure 18.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Refer to following chapter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure control</td>
<td>Chapter 2</td>
</tr>
<tr>
<td>Use of organ protective therapies</td>
<td>Chapter 2 and Chapter 4</td>
</tr>
<tr>
<td>Dietary sodium intake</td>
<td>Chapter 4 and Chapter 7</td>
</tr>
<tr>
<td>Regular exercise</td>
<td>Chapter 7</td>
</tr>
<tr>
<td>Dietary protein intake</td>
<td>Chapter 7</td>
</tr>
<tr>
<td>Management of anemia</td>
<td>Practice Point 3.1.2.</td>
</tr>
<tr>
<td>Management of diabetes</td>
<td>Practice Point 3.1.4.</td>
</tr>
</tbody>
</table>

*Figure 18. Measures for CKD management in people with autosomal dominant polycystic kidney disease (ADPKD).*

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

People with ADPKD tend to have a higher hemoglobin compared with other forms of CKD due to regional hypoxia driving production of hypoxia-inducible transcription factors, with HIF-1 and HIF-2 expressed in cyst epithelia and pericystic interstitial cells, respectively. Yet, some people with ADPKD may be at risk for iron deficiency and anemia due to recurrent bleeding into cysts, which may necessitate blood transfusions. Optimal management of both iron deficiency and anemia will limit the need for transfusion. Please refer to the *KDIGO Clinical Practice Guideline for Anemia in CKD* for specific guidance.
Practice Point 3.1.3: Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI) should not routinely be used to manage anemia in people with ADPKD.

Cyst growth is accompanied by regional hypoxia and induction of HIF-1α in cyst-lining epithelial cells. Induction of HIF-1α increases chloride-dependent fluid secretion and promotes a switch from oxidative phosphorylation to glycolysis, thereby promoting cyst expansion. HIF-1α levels are high in human and mouse ADPKD kidneys, and HIF-1α and HIF-2α expression levels correlate with cyst burden. In an experimental mouse model of ADPKD, HIF-PHI resulted in severe aggravation of the phenotype with rapid loss of kidney function. HIF-1α may also promote cyst growth in polycystic livers. There is no evidence regarding the benefits or harms of HIF-PHI in people with ADPKD.

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

Because of the high prevalence of type 2 diabetes (T2D), ADPKD and T2D frequently co-exist. People with ADPKD and T2D have been shown to have almost 2-fold larger kidney volumes as compared to matched people with ADPKD without diabetes. Glucose concentration has a strong impact on cyst growth of renal tubular cells within a collagen matrix as well as in embryonic kidneys deficient or competent for PKD1. Hyperglycemia aggravates cell proliferation and cyst formation in a mouse model of PKD induced by the knockout of the intraflagellar transport protein Ift88. Increasing evidence from preclinical animal models suggests that metabolic defects likely contribute to the pathogenesis of ADPKD.

The KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease, with the possible exception of SGLT2i, are applicable to people with ADPKD. Glycemic management with metformin when eGFR is ≥30 ml/min per 1.73 m² or with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) when eGFR is <30 ml/min per 1.73 m², when metformin is not tolerated or when treatment with metformin alone is not sufficient for optimal glycemic control are preferred in people with ADPKD and T2D. GLP-1 RA, like SGLT2i, have been shown to improve cardiovascular and kidney outcomes in people with T2D.

There is no clear evidence of specific benefits or harms from diabetic therapies in people with ADPKD with or without T2D, primarily because most clinical trials on cardiovascular and kidney outcome have excluded people with ADPKD and because clinical trials of diabetic therapies in ADPKD have been underpowered.

SGLT2i retard the progression of CKD in people with or without diabetes, but there are no data about use in people with ADPKD. Use of SGLT2i in ADPKD is presently not recommended because people with ADPKD were excluded from the clinical trials. The renal hemodynamic effects of SGLT2i (stimulating of tubuloglomerular feedback and lowering
glomerular hypertension and hyperfiltration) and their metabolic effects (like those of caloric restriction) may be protective in ADPKD. On the other hand, because of osmotic diuresis, SGLT2i increase the release of vasopressin which may promote cyst growth. The SGLT2i also induce marked glucosuria, increasing the risk for genitourinary fungal and bacterial infections. In a rat model of ADPKD, dapagliflozin caused osmotic diuresis, hyperfiltration, albuminuria, and an increase in kidney cyst volume compared with controls. A 12-month, randomized, double-blind, placebo-controlled trial (NCT05510115) will study the effect of empagliflozin on kidney volume and function in 50 people with ADPKD with eGFR 30–90 ml/min per 1.73 m². The use of SGLT2i after kidney transplant has in general been limited by concerns of infection and has not been specifically evaluated in post-transplant people with ADPKD.

GLP-1 RAs are thought to be kidney protective by lowering glucose and lipid levels, weight, blood pressure, and inflammation. They enhance insulin secretion, slow gastric emptying, and increase satiety thus leading to weight loss. They may be well suited to treat post-transplant diabetes by counterbalancing the immunosuppressive drug effects on insulin secretion and insulin resistance. No clinical trials in people with CKD or ADPKD without diabetes nor preclinical studies in rodent models of ADPKD have been performed.

Thiazolidinediones (pioglitazone and rosiglitazone) are antidiabetic drugs that activate the transcription factor peroxisome proliferator-activated receptor γ and adenosine monophosphate-activated protein kinase (AMPK). A randomized phase 1b crossover study of the insulin sensitizing thiazolidinedione pioglitazone in 18 people with ADPKD without diabetes did not detect harmful adverse effects nor a significant benefit slowing kidney growth or eGFR decline. This trial was based on preclinical studies showing that pioglitazone and rosiglitazone inhibit the expression of cystic fibrosis transmembrane conductance regulator (CFTR) and attenuate cyst growth in the PCK rat.

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.

Lipid management in CKD was comprehensively reviewed in the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Although no studies demonstrating a lipid-lowering benefit have been specifically conducted in people with ADPKD, reduced eGFR and albuminuria are strongly associated with cardiovascular morbidity and mortality. Lipid lowering therapy reduces CVD events in people with CKD. Two recent major guidelines have supported the use of the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease.

The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias have recommended aggressive lipid-lowering targets (low density lipoprotein <55 mg/dl [<1.4 mmol/l]) for
primary protection in people with CKD not on dialysis.\textsuperscript{242} However, due to concerns regarding safety and tolerability of using high-intensity statins in CKD, the Work Group agrees with the adoption of \textit{KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease} in people with ADPKD (Figure 19).\textsuperscript{220} The KDIGO Work Group did not recommend the treat-to-target strategy because it had never been proven beneficial in any clinical trial. In addition, higher doses of statins have not been proven to be safe in the setting of CKD. Therefore, the KDIGO Work Group recommended a “fire-and-forget” strategy for people with CKD (Recommendation 1.2 in the \textit{KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease}). Physicians may choose to perform follow-up measurement of lipid levels in people for whom these measurements are judged to favorably influence adherence to treatment or other processes of care.

The possible use of statins for the primary purpose of slowing the growth of polycystic kidneys, beyond their lipid lowering effect, is discussed in Chapter 4.

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tbody>
<tr>
<td>In adults aged &gt;50 years with CKD and eGFR &gt;60 ml/min/1.73 m(^2) (GFR categories G1–G2) we recommend treatment with a statin (1B).</td>
</tr>
<tr>
<td>In adults aged &gt;50 years with eGFR &lt;60 ml/min/1.73 m(^2) but not treated with chronic dialysis or kidney transplantation (GFR categories G3a–G5), we recommend treatment with a statin or statin/ezetimibe combination (1A).</td>
</tr>
<tr>
<td>In adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, we suggest statin treatment in people with one or more of the following (2A): • known coronary disease (myocardial infarction or coronary revascularization) • diabetes mellitus • prior ischemic stroke • estimated 10-year incidence of coronary death or non-fatal myocardial infarction &gt;10%</td>
</tr>
<tr>
<td>In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated (2A) In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued (2C). In adult kidney transplant recipients, we suggest treatment with a statin (2A).</td>
</tr>
</tbody>
</table>

\textbf{Figure 19. Recommendations from the KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease.}\textsuperscript{220} CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate

\textbf{Research recommendations}

- Studies are needed to assess the impact of new glucose-lowering therapies, such as SGLT2i and GLP-1 RA, and of thiazolidinediones on progression and complications of ADPKD.
Studies are needed to assess the role of erythropoiesis-stimulating agents including hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHI) in the treatment of anemia associated with ADPKD. Exploratory sub-analyses of major HIF-PHI trials are needed to compare the kidney function of people with ADPKD with other forms of CKD.

3.2. Kidney transplantation

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

People with ADPKD generally do well after transplantation, reflecting the nature of the disease. Outcomes are comparable to the general transplant population and typically better than those people with diabetic nephropathy. Thus, kidney transplantation is the preferred management option for people with ADPKD and kidney failure.243, 244

The principal cause of mortality in all forms of kidney failure is CVD. In an analysis of mortality in a large cohort from the United States Renal Data System, people with ADPKD had a mortality rate after transplant from all causes (including cardiac arrest, acute myocardial infarction, other cardiac disorders, cerebrovascular disease, infection, and malignancy) similar to that of other people with kidney failure due to other kidney diseases and lower than that of people with kidney failure due to diabetic nephropathy.244 Nevertheless, a number of post-transplant complications specific to ADPKD have been reported (Figure 20). Some of these complications, such as erythrocytosis or cardiac valvular disease, reflect ongoing progression of conditions associated with ADPKD that existed prior to transplant.245-250 Increased awareness of these issues and vigilant screening and management are required.

<table>
<thead>
<tr>
<th>Post-transplant complication</th>
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<tbody>
<tr>
<td>New-onset diabetes</td>
<td>Pooled RR 1.92; 95% CI: 1.36–2.70</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>ADPKD in 17% of patients with vs 6% without erythrocytosis p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Pooled relative risk (pooled RR: 1.56; 95% CI: 1.21–2.01)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Greater risk for worsening of tricuspid, mitral and aortic valve regurgitation</td>
</tr>
<tr>
<td>Aortic root dilatation</td>
<td>Greater risk for dilation of sinus of Valsalva and ascending thoracic aorta</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>3.8/1000 hospital admission in kidney transplant recipients with ADPKD compared to 0.9/1000 in kidney transplant recipients without ADPKD</td>
</tr>
<tr>
<td>Thromboembolic events (DVT, PE)</td>
<td>8.6% of 534 patients with ADPKD vs. 5.8% of 4779 patients without ADPKD after kidney transplantation (p = 0.009)</td>
</tr>
<tr>
<td>Skin cancers: SCC, BCC, melanoma</td>
<td>Adjusted ORs 1.22, 1.30, 1.21, respectively</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Weak evidence only</td>
</tr>
<tr>
<td>Cyst infection</td>
<td>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</td>
</tr>
<tr>
<td>Colon diverticulitis</td>
<td>Prevalence (2006–2013) in kidney transplant recipients with compared to without ADPKD (2.6% vs 0.8%)</td>
</tr>
</tbody>
</table>

Figure 20. Post-transplant complications that are more common in people with autosomal dominant polycystic kidney disease (ADPKD) than other forms of chronic kidney disease (CKD). BCC, basal cell
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.

Provision of a living donor transplant allows the elective performance of the transplant when the recipient is in optimal health status, avoids the need for creation of dialysis access, avoids potentially multiple years of waiting time for a deceased donor kidney transplant, and provides a greater likelihood of long-term allograft survival (KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors). Potential kidney transplant candidates should be referred for evaluation as a transplant candidate at least 12 months (or longer depending on local practices) before anticipated dialysis initiation to facilitate identification and work-up of living donors and plan for possible pre-emptive transplantation (KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation Recommendation 1.1.1). The physician should educate the candidate that evaluation of living donors may take longer than 12 months and that early identification of potential living donors is essential. Should a living donor not be available, timely referral to a transplant center is essential to allow listing of the candidate on the deceased-donor waiting list; the eligibility criteria for being placed on the waitlist depends on the country of listing.

Due to the likelihood of reduced availability for living, related donors in ADPKD families as the result of autosomal dominant inheritance, there is value in evaluation of the extended family, and the wider circle of friends, coworkers, and acquaintances. From the patient perspective, it is preferable for the physician to educate the patient about the benefits of evaluation of both family and other potential donors so that the patient can develop an outreach plan that fits within their own and their family’s values/culture. The patient must understand that it is to their benefit to find a living donor, which offers the best outcome if kidney failure is ever reached. If a person is diagnosed later in life or with declining eGFR, this conversation can occur as early as initial diagnosis because this is when the patient is most likely to share their diagnosis with their family, some of whom will ask about how they can help.

An evaluation of extended family or other potential donor candidates would allow assessment of blood types as a minimum requirement for a potential donor-recipient pair. Further, such discussions could include education regarding healthier donor lifestyles, including weight reduction, smoking cessation, heart-healthy diet, and behaviors to facilitate candidacy of potential kidney donors. (For more details, please refer to KDIGO Clinical Practice Guideline on...
Such evaluations will facilitate the education of potential kidney donors and transplant candidates about options, risks, and benefits of living donor kidney transplantation.

The performance of blood type- or HLA-incompatible living donor kidney transplants can be facilitated via kidney exchanges of 2 or more donor-recipient pairs, including altruistic donors in some countries. Timing and organization of such exchanges are managed by transplant centers and organ procurement organizations.\textsuperscript{251, 255}

**Practice Point 3.2.5: Excluding the diagnosis of ADPKD in potential living-related kidney donors is an important consideration.**

Chapter 1 presents the guidance to establish or to exclude a diagnosis of ADPKD. Ultrasound can generally be used for the initial screening, since CT angiography/urography or MRI which are used in most centers to evaluate the anatomy of the kidneys of potential donors, will provide confirmatory evidence to exclude a diagnosis of ADPKD.

**Practice Point 3.2.6: 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 BMI.**

Since end-stage ADPKD can result in up to 40 pounds (approximately 20 kg) of total kidney and liver weight, a BMI measurement based on height and weight alone may result in a BMI value that lies outside of the objective BMI criteria for acceptance into a kidney transplant program. For this reason, during the health-screening phase, the calculated kidney and liver weight should be subtracted from a patient’s total weight to arrive at a more accurate indication of patient health (Figure 21). This calculation assumes that 1 ml of kidney or liver volume is equivalent to 1 g of weight. Skinfold caliper measurements can also be used to estimate BMI.

**Figure 21. Calculations for estimated body mass index (BMI) in people with autosomal dominant polycystic kidney disease (ADPKD).** *Adjusted body weight subtracts the estimated total polycystic kidney and liver weights from the total weight, with a correction for the normal total kidney and liver weights. Normal kidney and liver weights vary with age and BMI (Typical Organ Weights.pdf (duke.edu)). † A reasonable approximation for total kidney weight is 0.27 kg for men and 0.23 kg for women and for liver, 1.6 kg for men and 1.3 kg for women. TKV, total kidney volume; TLV, total liver volume.
Recommendation 3.2.1: We suggest that native kidney nephrectomy in people with ADPKD receiving a kidney transplant should be performed only for specific indications where the benefit outweighs the risk (Figure 22) (2C).

Practice Point 3.2.7: Shared decision-making with patients pretransplant and multidisciplinary case conferencing should contribute to the decision regarding performing and timing of nephrectomy.

Practice Point 3.2.8: People with ADPKD should be treated with the same immunosuppressive protocols as other transplant recipients.

This recommendation places a higher value on the lack of identifiable benefit than on the safety and acceptability of nephrectomy in people with ADPKD. The recommendation is weak in the opinion of the Work Group because of the low certainty of evidence demonstrating no benefit of the procedure, facing limited concerns for safety associated with nephrectomy in people with ADPKD.

Figure 22. Potential indications for native kidney nephrectomy in people with autosomal dominant polycystic kidney disease (ADPKD) receiving a kidney transplant. *People with CKD should be asked for pain and volume related complaints in a structured manner, preferably using a questionnaire (e.g., the ADPKD-PDS, the ADPKD-IS and the GI symptom questionnaires).

Key information

Balance of benefits and harms

The evidence review found nine studies that compared people with ADPKKD who had nephrectomy with those who did not.256-265 None of these studies demonstrated clear benefit of nephrectomy on critical post-transplant outcomes, particularly graft loss or all-cause mortality. There was an absence of clear excess of major surgical complications, although individual and aggregated studies provided imprecise estimates. One database analysis found a higher risk of blood transfusion if nephrectomy was conducted at the time of transplantation.259 One small study reported decreased frequency of kidney cyst infection and of persistent hypertension
among those undergoing nephrectomy for ADPKD at the time of kidney transplantation, but these outcomes were not reported by other studies. However, there are situations where native kidney nephrectomy may be warranted, including pain, bleeding, nephrolithiasis, infection, suspected cancer, etc. (Figure 22). The indication may also determine the timing of the nephrectomy. Nephrectomy for a suspected cancer or after a recent infection should be performed before transplantation.

**Certainty of evidence**

The overall certainty of evidence was graded as low primarily due to the methodological limitations of the mostly retrospective, unadjusted analyses for critical outcomes of interest (Supplementary Table S5). The lack of adjustment (or randomization) was of particular concern in these studies where there are likely to be numerous inherent differences among patients and clinicians who choose to undergo nephrectomy and those who do not. This concern resulted in low certainty of evidence regarding the outcomes critical for decision-making, graft loss and long-term all-cause mortality, and the important outcome delayed graft function. Only single small studies, or no study, reported on several critical outcomes, precluding conclusions. The critical outcomes allograft function, quality of life (QoL), renal cell carcinoma (in the native kidney), and the important outcome cyst infections (in the native kidney) were reported by single small studies with serious methodological limitations; thus, yielding very low certainty of evidence. The important outcomes such as surgical complications were relatively rare such that studies were underpowered and provided imprecise effect size estimates, even in aggregate, and, thus, very low certainty of evidence; however, a large study, with some (not serious) limitations, provided low certainty of evidence regarding risk of requiring a blood transfusion. Studies did not report outcomes for numerous critical and important outcomes. Based primarily on the low certainty of evidence for the critical outcomes graft loss and death, together with the low certainty of evidence for the surgical complication of transfusion, we concluded that overall, there is low certainty of evidence (Level C).

**Values and preferences**

The choice to proceed with an invasive surgical procedure requires careful consideration by all parties involved. This recommendation places relatively higher value on avoiding procedures that do not have clearly identifiable clinical or patient benefit. While recommending not to undertake nephrectomy as a routine procedure for most people with ADPKD without a specific indication, careful multidisciplinary discussion should be undertaken when the procedure is being considered. The recommendation is overall weak as the Work Group judged that the majority of well-informed people would not choose to undertake routine native kidney nephrectomy and would only consider it if there was a specific or compelling indication to do so.

**Resource use and costs**

All surgical procedures entail health service utilization and the potential experience of complications, even if these are infrequent. Nephrectomy has impacts for resources and costs to both health systems and people.
Considerations for implementation

A multidisciplinary discussion involving all relevant team members and the patient should be convened in circumstances where native kidney nephrectomy is being considered for a person affected by ADPKD.

Physicians need to understand that most side-effects (pain, recurrent infections, cyst bleeds, acid reflux, etc.) in people with ADPKD are related to their cyst-swollen, enlarged kidneys. As a result, people will often enter the nephrectomy discussion in favor of the procedure. During this discussion, it is important for physicians and/or surgeons to educate patients that it is common for native ADPKD kidneys to shrink up to 30% in the first year after transplant, which may impact many side effects that people experience.²⁶⁶, ²⁶⁷

There is no convincing evidence to support a different benefit or risk profile for people needing a transplant because of ADPKD than those who have other CKD. One study suggests a benefit of sirolimus to reduce the growth of polycystic livers after transplantation.²⁶⁸ An analysis of a limited number of people with a kidney transplant and ADPKD showed that cystic kidney volumes regressed significantly more on a sirolimus-based than on a calcineurin inhibitor-based immunosuppressive regimen. RCTs of mammalian target of rapamycin (mTOR) inhibitors in non-transplant people with ADPKD have been mostly ineffective in slowing progression (Chapter 4).²⁶⁹

Rationale

This recommendation was based on systematic review of 9 studies that examined all-cause mortality, graft loss, and delayed graft function at >1 year and surgical complications up to 1 year post-operation. There was no identifiable benefit for any of the efficacy outcomes even though there was no apparent increase in critical surgical complications. On balance, the absence of benefit as well as surgical complications guided the rationale of this recommendation, although the Work Group recognizes that individual scenarios may clinically arise where nephrectomy may be considered in the context of potential surgical complications.

Recommendation 3.2.2: We suggest unilateral rather than bilateral native kidney nephrectomy in people with ADPKD, when appropriate (2D).

This recommendation places a high value on the relative absence of evidence to guide making any specific recommendation for or against bilateral rather than unilateral nephrectomy, with heuristic experience indicating that clinicians undertake great caution and consideration in such a context if clinically indicated. The recommendation is weak in the Work Group opinion because of the very low certainty or lack of evidence addressing the comparison of bilateral vs. unilateral nephrectomy in people with ADPKD.
Key information
Balance of benefits and harms

This recommendation is based upon a single, small report of unilateral compared to bilateral nephrectomy in the setting of kidney transplantation for people with ADPKD. The only relevant information to this recommendation was regarding surgical complications which did not indicate clear excess complications of bilateral versus unilateral nephrectomy, though this is likely limited by cohort size rather than confidence of true noninferiority. Given the lack of evidence to support the benefit of bilateral over unilateral nephrectomy, the Work Group recommends the less nephrectomy surgery to minimize risk of complications or negative patient outcomes. There can be additional risks with bilateral nephrectomy, such as refractory postoperative hypotension. However, there are exceptional situations where bilateral nephrectomy may be warranted, including infection, nephrolithiasis, bleeding, pain, suspected cancer, etc. (Figure 22).

Certainty of evidence

The overall certainty of evidence was graded as very low (Supplementary Table S6). Only a single, small study provided separate data for people undergoing either bilateral or unilateral surgery, but the study was primarily comparing hand-assisted laparoscopic nephrectomy with open nephrectomy, with separately reported data for bilateral or unilateral nephrectomies. Thus, there were serious limitations regarding the comparison of bilateral versus unilateral nephrectomy. The study reported only surgical complications, which had a very imprecise effect size estimate. Therefore, there was very low certainty evidence (Level D). The certainty of evidence was also very low for surgical complications.

Values and preferences

This choice to proceed with an invasive surgical procedure requires careful consideration by all parties involved, and the Work Group suggests that this is especially the case with bilateral compared to unilateral nephrectomy. This recommendation places a high value on the absence of clearly identifiable clinical or patient benefit and a lack of evidence suggesting greater incidence of complications between the procedures. Consequently, it is advised that a clear indication be present for a discussion of these procedures and that a multidisciplinary discussion be undertaken when bilateral nephrectomy is being considered. The recommendation is weak as the Work Group judged that the majority of well-informed people would not choose to undertake bilateral native kidney nephrectomy at the time of transplantation and would only consider it if there was a specific or compelling indication to do so.

Resource use and costs

All surgical procedures entail health service utilization with impacts for resources and costs to both health systems and people. Confidence around the relative benefits and complications of proceeding versus not proceeding with such a potentially invasive surgical procedure need to be transparently discussed in each individualized instance.
Considerations for implementation

A multidisciplinary discussion involving all relevant team members in addition to incorporating the patient perspectives should be convened in circumstances where native kidney nephrectomy is being considered for a person affected by ADPKD.

Rationale

This recommendation is based on the lack of evidence supporting the benefit from bilateral nephrectomy and the Work Group concern about potential increased complications from performing bilateral nephrectomy. This concern persisted despite a single study reaching uncertain conclusions about the benefits and complications. This study indicated that bilateral nephrectomy can be technically performed rather than unilateral nephrectomy for people affected by ADPKD, though benefits and complications are insufficiently clear. On balance, the absence of benefit in the presence of any surgical complication potentiality guided the rationale of this recommendation whilst still recognizing that alternate and individual scenarios may clinically arise where bilateral rather than unilateral nephrectomy may be considered though required consideration in context of potential surgical complications.

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

Practice Point 3.2.9: Nonsynchronous native kidney nephrectomy and shared decision-making may be considered given additional potential challenges associated with nephrectomy undertaken synchronously with kidney transplantation.

This recommendation places a high value on the potential benefit of all-cause mortality for nephrectomy at the time of or after kidney transplantation compared to nephrectomy pretransplantation, and a low value of the comparable surgical complications associated with the timing of nephrectomy. The recommendation is weak in the Work Group opinion because of the low certainty of evidence demonstrating a benefit of the timing of nephrectomy.

Key information

Balance of benefits and harms

The evidence review found 7 studies that evaluated people with ADPKD who underwent nephrectomy, comparing different timing of the nephrectomy (pretransplant, with transplant, or post-transplant). Most studies reported the critical outcomes of graft loss and all-cause mortality, with fewer studies reporting surgical complications. None of the studies individually found a significant difference in critical outcomes, but a meta-analysis of 5 studies found a nearly significantly association of pretransplant nephrectomy with increased risk of all-cause mortality (odds ratio [OR]: 1.87; 95% CI: 0.96–3.63; P=0.065); however, all studies provided unadjusted estimates. Meta-analysis of 4 studies found no significant difference in graft loss (OR: 1.17; 95% CI: 0.60–2.27). Based primarily on 1 large, adjusted database analysis (together with a small unadjusted study), pretransplant nephrectomy may be associated with an increased
risk of in-hospital post-transplant death (OR: 6.61; 95% CI: 1.25–34.9), but comparisons of other surgical complications were imprecise. The experience and qualifications of the surgical team are thought to be important but are not addressed in these studies.

While there is no evidence indicating excess risk of mortality or major complications in association with undertaking native kidney nephrectomy at the same time as kidney transplantation in ADPKD, there may be additional aspects which should be taken into consideration. Factors such as longer operative time and increased risk of blood transfusions have been noted. These likely have a role in personalized and shared decision-making, with nonsynchronous native kidney nephrectomy being one strategy to minimize risk and likelihood of them being experienced.

Certainty of evidence

The overall certainty of evidence was graded as low primarily due to the methodological limitations of the mostly retrospective, unadjusted analyses for critical outcomes of interest (Supplementary Table S7). The lack of adjustment (or randomization) was of particular concern in these studies where there are likely to be numerous inherent differences among patients and clinicians who choose different timing of nephrectomy and possible differences in the experience of the surgeons who conduct the different surgeries. This concern resulted in low certainty of evidence regarding the outcome critical for decision-making, long-term all-cause mortality. In addition to serious methodological limitations, effect estimates were imprecise for the critical outcome graft loss and the important outcomes of major surgical complications (except for surgical death). For the critical outcome surgical death (Clavien Dindo category V), the effect size estimated was based primarily on one large study (with some methodological limitations), with a second, small, highly imprecise study; thus, we determined the evidence was sparse (based on a single study), yielding low certainty of evidence. This large study similarly provided low certainty of evidence regarding important outcome risk of transfusion at the time of transplantation. Primarily because of limited data reporting on allograft function from studies with serious methodological limitations, there was very low certainty of evidence for the critical outcome. A single small study with serious methodological limitations provided very low certainty regarding the important outcome delayed graft function. Studies did not report outcomes for numerous critical and important outcomes. Based primarily on the low certainty of evidence for the critical outcome death (both long-term and post-transplant), together with the low certainty of evidence for the surgical complication of transfusion, we concluded that overall, there is low certainty of evidence (Level C).

Values and preferences

Planning for and choosing to undertake an invasive surgical procedure requires careful consideration. This recommendation places relatively higher value on the potentially improved all-cause and in-hospital mortality benefits if nephrectomy is undertaken with or after kidney transplantation for ADPKD. It also places a low value of the comparable surgical complications associated with the timing of nephrectomy. We reiterate earlier recommendations to not undertake nephrectomy as a routine procedure for the majority of people with ADPKD without a
specific indication, and that if nephrectomy is being considered then careful multidisciplinary
discussion is undertaken. The recommendation is weak as the Work Group judged that most
well-informed people would not choose to undertake routine native kidney nephrectomy before
kidney transplantation in the absence of a specific or compelling indication to do so.

Resource use and costs

Kidney transplantation itself can be complicated and resource intensive, both medically
and surgically. The addition of a further significant surgical procedure within this period would
have additional implications for resource utilization that may not be necessarily synergistic. In
the absence of a clear indication, potential deferral of nephrectomy might be considered.

Considerations for implementation

A multidisciplinary discussion involving all relevant team members in addition to
incorporating the patient perspectives should be convened in circumstances where native kidney
nephrectomy is being considered for a person affected by ADPKD. Experience of the surgical
team needs to be taken into consideration.

Rationale

This recommendation was based on systematic review of 7 studies that examined all-
cause mortality, graft loss, delayed graft function at >1 year, and surgical complications. There
was no clear benefit in outcomes. One large database analysis suggested an increased risk of in-
hospital mortality at the time of transplantation with pretransplant nephrectomy, but overall,
studies found no apparent increase in other major surgical complications. There was a trend
towards improved all-cause mortality when nephrectomy was undertaken with or after kidney
transplantation in people with ADPKD rather than before. The absence of benefit in the presence
of surgical complications guided the rationale for this recommendation; however, the Work
Group recognizes that alternate and individual scenarios may clinically arise where nephrectomy
may be considered though required consideration in context of potential surgical complications.

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

This recommendation places a high value on the less invasive nature and the safety of hand-
operated laparoscopic nephrectomy and places a low value on the lack of clinical benefit of
different surgical approaches to nephrectomy in ADPKD. The recommendation is weak in the
Work Group opinion because of the low certainty of evidence addressing all identified surgical
complications and lack of evidence for clinical benefit.

Key information

Balance of benefits and harms

This recommendation is based upon 3 studies examining surgical complications in
studies comparing hand-operated laparoscopic nephrectomy versus open nephrectomy in people
with ADPKD.187, 271, 272 None of these studies demonstrated clear benefit in terms of either all
combined or differing Clavien-Dindo grades of surgical complications, however hand-operated laparoscopic nephrectomy was associated with fewer people requiring transfusion (OR: 0.32; 95% CI: 0.12–0.82). The studies did not report clinical outcomes other than surgical complications.

Certainty of evidence
The overall certainty of evidence was graded as very low primarily due to the methodological limitations of the mostly retrospective, unadjusted analyses for critical outcomes of interest, imprecision, and a lack of evidence for outcomes other than surgical complications (Supplementary Table S8). The lack of adjustment (or randomization) was of particular concern in these studies where there are likely to be numerous inherent differences among patients and clinicians who choose different surgical procedures. Due to low event rates in small studies, there was very low certainty of evidence for the critical outcome post-operative death and the important outcomes any surgical complication and Clavien Dindo grade ≥IV complication. The effect estimates were more precise perioperative transfusions and Clavien Dindo grade ≥III complication, allowing low certainty of evidence for these important outcomes. Given the lack of evidence for outcomes other than surgical complications, and very low certainty of evidence for the more important surgical complications, we concluded that overall, there is very low certainty of evidence (Level D).

Values and preferences
This recommendation places relatively higher value on the potential that the experience of a laparoscopic rather than open surgical procedure is likely to be preferred by many people in terms of improved recovery time and cosmesis. Although, notably, none of the studies comparing surgical techniques addressed this issue. Given that neither surgical approach appears inferior to the other in terms of surgical complications, the value of decreased transfusion requirements with hand-operated laparoscopic nephrectomy is of heightened importance. The recommendation places a low value on the lack of clinical benefit of different surgical approaches to nephrectomy in ADPKD. However, we reiterate earlier recommendations to not undertake nephrectomy as a routine procedure for most people with ADPKD without a specific indication, and that if it is being considered, careful multidisciplinary discussion is undertaken. The recommendation is weak as the Work Group judged that the majority of well-informed people would prefer hand-operated laparoscopic nephrectomy if there was a specific indication for it and the surgical approach was feasible in their individualized circumstance.

Resource use and costs
Careful consideration of clinical urgency, indication, and circumstance is required in the context of available skillsets and equipment for different surgical approaches to nephrectomy. Where feasible, the decreased rate of transfusion and potential for earlier ambulation or discharge associated with laparoscopic approaches might offer resource use and cost benefits.
Considerations for implementation

A multidisciplinary discussion involving all relevant team members in addition to incorporating the patient perspectives should be convened in circumstances where native kidney nephrectomy is being considered for a person affected by ADPKD. Experience of the surgical team needs to be taken into consideration. It is recognized that hand-operated laparoscopic nephrectomy may not be universally available due to lack of surgical experience or unavailability of necessary equipment.

Rationale

This recommendation was based on systematic review of 3 studies that examined surgical complications related to hand-operated laparoscopic compared with open nephrectomy. There was not an identifiable difference between approaches in various grades of surgical complications, or all surgical complications combined, although there was a decreased likelihood of requiring transfusion. This lower likelihood of transfusion as well as a less invasive surgical approach are what justified this recommendation. The Work Group still recognizes that alternate and individual scenarios may clinically arise where open nephrectomy may be considered more appropriate.

Practice Point 3.2.10: Evaluation for RCC in pretransplant people with ADPKD should be individualized and imaging of the kidneys (e.g., abdominal MRI) within 1 year prior to transplantation should be considered.

The risk of significant RCC is not thought to be increased in people with ADPKD receiving dialysis or post-transplant compared to people with other kidney disease etiologies in majority of the studies. Nevertheless, a recent retrospective analysis from Taiwan found an increased likelihood of RCC (25 cases in PKD vs. 5 controls [without CKD], fully adjusted hazard ratio of 5.26; 95% CI: 2.01–13.8), in a cohort of people with ADPKD without reduced GFR or kidney failure. Of 79 patients of whom 50 had kidney failure and were on hemodialysis or had received a transplant for >1 year, 11 of 89 kidneys were diagnosed with carcinoma with a mean diameter of 18 mm. In another study, 16 incidental RCC were found in 301 native ADPKD kidneys (5.3%). While the approach to screening transplant candidates before or after transplantation has not been standardized, we advise abdominal MRI to screen for solid kidney lesion within 1 year prior to transplantation. MRI without intravenous contrast is the appropriate first imaging test for this indication in people with kidney failure, and especially if dialysis dependent. Unenhanced MRI has significant advantages over noncontrast MRI due to its superior soft tissue contrast resolution, specifically its ability to depict fluid, fat, and soft tissue as distinct signal intensities. Unenhanced MRI can confirm simple cysts as well as typical T1 hyperintense hemorrhagic and proteinaceous cysts. While the risk of nephrogenic systemic fibrosis (NSF) is sufficiently low (or perhaps nonexistent) when using a standard or lower than standard dose of a group II gadolinium-based contrast agent (GBCA), contrast should only be administered if necessary. Noncontrast MRI has significant advantages over noncontrast CT due to its superior soft tissue contrast resolution, specifically its ability to depict fluid, fat, and soft tissue as distinct signal intensities. Unenhanced MRI can confirm simple cysts as well as typical T1 hyperintense hemorrhagic and proteinaceous cysts. Solid lesions should show more intermediate T1 and T2 signal intensities and may also be recognized by their appearance on diffusion-weighted imaging (DWI). If a solid lesion is suspected on noncontrast MRI and is not an
angiomyolipoma, consideration may be given to GBCA administration if a group II agent is available at the imaging center. In addition to confirming that a suspected solid lesion is enhancing, the contrast-enhanced exam provides added value for local tumor staging and evaluation for metastasis. Although contrast-enhanced ultrasound of a target lesion could also be considered, lesion localization and confident visualization with ultrasound is often markedly limited in ADPKD due to kidney size and multiplicity of cysts.

Research recommendations

- New and ongoing cohort studies and registries of people with ADPKD should analyze outcomes related to native kidney nephrectomy as well as the impact of the technique used (unilateral or bilateral).
- Studies are needed to assess the impact of unilateral nephrectomy on residual kidney function.
- Large scale evaluation studies across multiple areas should be undertaken to evaluate nephrectomy in people with ADPKD, incorporating clinical, patient-centric, and health economic outcomes. Given the clinical equipoise, randomized controlled trials would be preferred and would provide the strongest evidence.
- Research is needed into the development of objective criteria for determining appropriateness for nephrectomy.
- An RCT is needed to compare simultaneous versus post-transplant nephrectomy for volume space restriction. Alternative strategies for kidney size reduction (e.g., embolization) should also be studied.
- Studies are needed to better understand the events (evolution of kidney size, specific complications, etc.) associated with retained native ADPKD kidneys after onset of KRT.
- A registry analysis is needed to assess the incidence of post-transplant complications in ADPKD versus non-ADPKD and impact on long-term outcomes.
- More evidence is needed regarding the risk of RCC in people with ADPKD receiving dialysis or post-transplant compared to people with other kidney disease etiologies. Research is needed to identify the optimal protocol for detection of RCC in people pre- and post-transplant and those on dialysis.
- Research is needed to define the criteria for using ADPKD kidneys for transplantation. Follow-up after transplantation should be evaluated in a global registry.
- Long-term registry studies are needed on the development of clinically significant RCC in people with ADPKD on dialysis and with a transplant.
- Studies are needed to determine incidence and severity of kidney-related bleeding complications in people with ADPKD receiving systemic anticoagulation on dialysis or after transplantation.
- Studies to determine the impact of mTOR inhibitors to slow the growth of kidney or liver volume after transplantation.
3.3. Kidney replacement therapy
Practice Point 3.3.1: Shared decision-making between physician and patient should be undertaken for choice of dialysis modality.

If multiple dialysis modes (in-center hemodialysis [HD], home HD, continuous ambulatory, and/or automated peritoneal dialysis [PD]) are available to a person with ADPKD, a shared decision-making model between physician and the patient offers the best chance at optimal patient satisfaction. The prescribed dialysis mode is ideally a decision that is personalized to the underlying health of a particular person, likelihood of transplant, caregiver availability, lifestyle, life participation plans, and desire for autonomy. Shared decision-making ensures that patients make informed decisions that reflect their values, preferences, and priorities. Lack of shared decision-making often results in poor patient satisfaction with the treatment.282

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 hemodialysis and supportive therapies, such as anticoagulation, should be the same as for people without ADPKD.

This recommendation places a high value on the most appropriate care to balance benefits and harms in people with ADPKD when making the choice of dialysis modality and a low value on the lack of data on several important outcomes. Outcomes are similar between HD and PD. However, the recommendation is weak due to the low certainty of evidence.

Key information
Balance of benefits and harms

This recommendation is based on a pair of systematic reviews conducted of studies with ≥1 year follow-up directly comparing either PD and HD in people with ADPKD or PD in people with either ADPKD or other types of CKD. Four studies were identified that compared people on PD with people on HD (Supplementary Table S9).283-286 Three of these studies plus an additional 9 studies compared people with ADPKD receiving PD with other patients also receiving PD. The 4 studies comparing modalities reported on all-cause mortality, tolerability of the dialysis modality, and harms. The 12 studies of people on PD comparing causes of kidney failure reported the same outcomes, but also dialysis efficiency and residual kidney function. Studies
found no significant difference in all-cause mortality between PD and HD (summary effect size: 0.95; 95% CI: 0.58–1.56) (Figure 23).

Among the 12 studies of people undergoing PD, there were no significant differences between people with and without ADPKD with regard to dialysis dose (Kt/V), peritoneal leakage, peritonitis, switch to hemodialysis, technique failure, exit site infection, or mortality (Supplementary Table S10). Abdominal hernias were more common in ADPKD. Median time to technique failure for ADPKD was 6.2 years versus 6.5 years without ADPKD. Median time to death for ADPKD was 6.04 years versus 5.57 years without ADPKD. No studies addressed QoL, functional status, psychosocial issues, or pain.
Figure 23. Unadjusted (a) and adjusted (b) all-cause death of peritoneal dialysis (PD) versus hemodialysis (HD) in autosomal dominant polycystic kidney disease (ADPKD). adj, adjusted; HR, hazard ratio; OR, odds ratio
There was no apparent mortality difference between PD versus HD. More people switched from PD to HD than HD to PD in both the PKD and non-PKD populations (Supplementary Table S9). Hospitalizations for infection in people receiving PD compared to HD were significantly higher (58% vs. 44%), and there was a nonsignificant trend for more people receiving PD to have surgical intervention for hernias (7% vs. 4%) in 1 study.\textsuperscript{286}

**Certainty of evidence**

The overall certainty of evidence was graded as low for both the comparison of PD versus HD in people with ADPKD and the comparison of people with ADPKD and other people with CKD receiving PD. Many studies (particularly those comparing people with ADPKD and other types of CKD) did not adjust for inherent differences either between people who choose different dialysis modalities or who have different types of CKD.

For the comparison of dialysis modalities among people with ADPKD (Supplementary Table S9), the only outcome critical for decision-making that was reported by more than 1 study was all-cause mortality. The outcome had low certainty of evidence because the studies had some methodological limitations (related to method for adjustment for confounders or lack of adjustment) and, even in aggregate, a somewhat imprecise effect estimate. The other reported critical outcome, peritonitis, was reported by a single study with no methodological limitations, also providing low certainty of evidence (the highest possible level of certainty for a finding that has not been replicated). The studies reporting on the important outcome tolerability mostly reported only on switching from PD to HD (not vice versa), which meant that the studies had methodological limitations, indirectness of the outcomes, and incomplete reporting. However, there was a large, implied difference in tolerability among those on PD versus HD. Thus, overall, for tolerability, there was low certainty of evidence. A single small study reported on the important outcome risk of hernias, providing very low certainty of evidence. Studies did not report outcomes for numerous critical and important outcomes. Overall, based primarily on the low certainty of evidence for the critical outcomes mortality and peritonitis, we concluded that there is low certainty of evidence for the direct comparison of PD versus HD in people with ADPKD (Level C).

For the comparison of people with ADPKD or other types of CKD who are receiving PD (Supplementary Table S10), we found moderate certainty evidence for both the outcome critical for decision-making peritonitis and the important outcome tolerability. For both outcomes, numerous studies, with a large number of people (mostly without ADPKD) had some methodological limitations (pertaining to how confounders were adjusted for or for lack of adjustment), but yielded consistent, direct, and precise summary estimates. The studies reporting the critical outcome all-cause mortality had inconsistent findings; thus, there was low certainty of evidence for this outcome. The other critical outcome with data, residual kidney function, was reported by only a single study with serious methodological limitations; thus, with very low certainty of evidence. The two other important outcomes with data, dialysis efficiency and abdominal wall hernia, had serious methodological limitations and were, thus, deemed to have low certainty of evidence. Studies did not report outcomes for numerous critical and important
outcomes. Overall, while there was moderate certainty for the critical outcome mortality (and the important outcome tolerability), given the low certainty of evidence all-cause mortality and lack of evidence for most other critical outcomes, we concluded that there is low certainty of evidence (Level C) comparing PD in people with ADPKD with other people.

Values and preferences
The choice of PD versus HD is an important decision in a person with kidney failure due to ADPKD. There has been clinical consideration that PD may be disadvantageous in the context of ADPKD due to risk of peritonitis caused by diverticular disease, reduced dialysis adequacy, and risk of hernias related to kidney size, increased abdominal pressure, and reduction in abdominal volume.285, 286 This must be balanced against patient preference and certain advantages of PD related to autonomy, QoL, and preservation of residual kidney function. Although there was increased hospitalization for infection and possibly more surgical intervention for hernia in people receiving PD, there was no apparent increase in mortality.

Resource use and costs
The availability of HD in low income countries may be limited, and PD offers greater access to receive KRT. PD is generally cheaper than HD and offers greater access to KRT in countries or localities with resource constraints or where HD slots are limited. Home HD is less expensive than in-center HD. PD does not require the same levels of expertise and hardware that are required to run an HD unit, which may be important in low income countries.

Considerations for implementation
There are no specific considerations for implementation, but shared decision-making is important.

Rationale
Given the low certainty of evidence, it was difficult to compare the potential benefits of one dialysis modality versus another in people with ADPKD. Also with low certainty, the evidence does not demonstrate specific harms associated with PD in ADPKD except for the increased likelihood of abdominal hernia in ADPKD. The choice of PD versus HD should be determined by patient factors, such as kidney and liver volume, preferences, availability of facilities and dialysis modalities. People with ADPKD and a history of abdominal hernia or colonic diverticula should consider with their dialysis provider whether future risk of developing specific complications (e.g., abdominal hernia, peritonitis) with the use of PD is acceptable.282

Research recommendations
- Better quality studies are required to address outcomes comparing PD versus HD in people with ADPKD, such as dialysis efficiency, residual kidney function, BP control, QoL, functional status, psychosocial well-being, kidney pain, bulk symptoms, and kidney size.
- Studies are needed to evaluate the specific impact of total kidney and liver volumes on the effectiveness, tolerability, safety of PD, and the likelihood of development of
abdominal hernias and other abdominal complications in people with ADPKD treated by PD.

- Further studies are needed to evaluate the advantages and disadvantages of continuous ambulatory peritoneal dialysis (CAPD) versus continuous cycling peritoneal dialysis (CCPD) and home or in-center HD in ADPKD.
CHAPTER 4. THERAPIES TO DELAY THE PROGRESSION OF KIDNEY DISEASE

Kidney failure is the major cause of disability and death in ADPKD. In most people, kidney failure is preceded by the progressive decline in the eGFR during the second, third, and fourth decades (Figure 24). Thus, the primary goal of medical treatment is to delay the onset of kidney failure.

Figure 24. Schematic diagram depicting the life journey and therapeutic considerations of a hypothetical person with autosomal dominant polycystic kidney disease (ADPKD) and rapidly progressive disease. At birth and during early childhood the kidneys may be macroscopically normal, and the diagnosis is typically made by a screening ultrasound at or after age 18. With age, the frequency of clinical manifestations increases, as depicted by the change in gradient of the blue bars: Hypertension is most commonly detected from about age 25 years as shown by the red square in the clinical manifestation bars; episodes of kidney/abdominal/back pain starting at about age 30 years; and onset of chronic kidney disease (CKD) G4-G5 from about age 50 years. Lifestyle interventions, blood pressure reduction, and consideration of tolvaptan initiation by a nephrologist (after confirming high-risk for progression, between CKD G2-G3) slows the progression of kidney function decline. The dotted line depicts the fall in the glomerular filtration rate. The duration of each CKD Stage (between G2-G5 and before dialysis or kidney transplantation) is about 2-10 years in length, as depicted by the progressive colors from tan (G1) to red (G5D). Commencing drug intervention during CKD G1 is the most effective strategy to slow the progression of kidney disease. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CKD, chronic kidney disease (stage).
As outlined in Chapter 7, lifestyle interventions that are advised (including smoking cessation, achieving BMI <25 kg/m², dietary sodium restriction (<2 g of sodium per day [or <90 mmol of sodium per day, or <5 g of sodium chloride per day]), and avoidance of factors causing AKI) should be implemented in all people with ADPKD, due to disease-specific effects on reducing kidney cyst growth.119, 120, 296, 297

*Inhibition of arginine vasopressin (AVP)*

Pharmacological interventions targeting the action of the antidiuretic hormone arginine vasopressin (AVP) are presently the cornerstone of treatment in people with ADPKD at risk of rapid disease progression. Preclinical data, obtained both *in vitro* and *in vivo*, have identified that AVP has a pathological role in ADPKD promoting kidney cyst growth during the postnatal period.298, 299 From a therapeutic viewpoint, the effects of circulating AVP on kidney cyst growth in ADPKD can be modified by at least 2 approaches that are not mutually exclusive: (i) pharmacological blockade of vasopressin-2 (V₂) receptors using tolvaptan (note that other V₂ receptor antagonists are available but only the efficacy tolvaptan has been evaluated in ADPKD); and/or (ii) increased water intake in excess of dietary solute consumption (Table 5).199, 300
<table>
<thead>
<tr>
<th>Factors</th>
<th>Increased water intake</th>
<th>V$_2$ receptor antagonist (Tolvaptan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Suppresses AVP release by lowering plasma osmolality</td>
<td>Selective blockade of AVP on V$_2$ receptors</td>
</tr>
<tr>
<td>Administration</td>
<td>Drinking water during waking hours</td>
<td>Split-dose tablet (2–3 in morning; 1-3 in evening to minimize nocturia)</td>
</tr>
<tr>
<td>Effect on water intake</td>
<td>Voluntary increase (≥2 liter/day)</td>
<td>Involuntary increase due to thirst and aquareesis (&gt;3–7 liter/day)</td>
</tr>
<tr>
<td>Effect on circulating AVP</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Potential indication for use in ADPKD</td>
<td>All people with eGFR &gt;30 ml/min per 1.73 m$^2$</td>
<td>Selected high-risk groups due to cost and side-effect considerations</td>
</tr>
<tr>
<td>Efficacy to ↓ urine osmolality to 300 mOsmol/kg</td>
<td>~50%</td>
<td>~70% of ADPKD participants over 3 years treatment in the TEMPO trials</td>
</tr>
<tr>
<td>Efficacy to ↓ TKV in ADPKD</td>
<td>No</td>
<td>Yes (TEMPO 3:4)</td>
</tr>
<tr>
<td>Efficacy to ↓ long-term eGFR decline</td>
<td>No data on risk reduction for CKD G5</td>
<td>Yes (~1 ml/min per 1.73 m$^2$) No data on risk reduction for CKD G5</td>
</tr>
<tr>
<td>Adherence to treatment</td>
<td>~50%</td>
<td>~70% in a 3-year clinical trial; but unknown in ‘real-world’ settings</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Long-term adherence is poor Pollakiuria, polyuria Reversible mild hyponatremia (1/1000 patients)</td>
<td>Thirst/dehydration Pollakiuria, polyuria Blood tests (every 1 to 3 months) Hyponatremia; hyperuricemia Risk of hepatotoxicity (1/3000 patients) Restricted access and cost</td>
</tr>
<tr>
<td>Advantages</td>
<td>Access and low cost</td>
<td>Standard dose Better 24-hour inhibition</td>
</tr>
</tbody>
</table>

Table 5. Different approaches to reduce arginine vasopressin (AVP) activity in autosomal dominant polycystic kidney disease (ADPKD). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes

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 aged 18-55 years with an estimated glomerular filtration rate (eGFR) ≥25 ml/min/1.73 m$^2$ who have or are at risk for rapidly progressive disease (Figure 25) (IB).
This recommendation places a high value in slowing the progression of kidney disease and preventing kidney failure. This needs to be balanced against the risks of initiating treatment with tolvaptan. In an evidence-based review of RCTs in people at high risk for progression, tolvaptan demonstrated high certainty evidence for slowing progression of kidney disease with the greatest benefit in the subgroup that were ≤55 years old with an eGFR ≥25 ml/min per 1.73 m².

Additional benefits were a reduction in the incidences of kidney pain and UTI. Shared and individualized decision-making should be undertaken when deciding to initiate tolvaptan in all people with ADPKD, including those older than 55 years old.

Figure 25. The Kidney Disease: Improving Global Outcomes (KDIGO) algorithm to decide to whom to prescribe tolvaptan. *Rapid disease progression is defined as reaching or expected to reach kidney failure due to autosomal dominant polycystic kidney disease (ADPKD) before the age of ~60 years, the average age at which untreated people with ADPKD reach kidney failure. The age of ~60 years is based on multiple cohort studies (ERA-EDTA, mean age 58 years; Genkyst cohort 61.7 years; Mayo PKD Database 62 years; Korea national cohort 62 years; ANZDATA registry 60 years which has been stable since the 1990s. †In case of likely alternative explanations for estimated glomerular filtration rate (eGFR) loss (e.g., vascular disease, uncontrolled hypertension, diabetic nephropathy, proteinuria ≥1 g/d), initiation of tolvaptan should be reconsidered even in the presence of rapid eGFR decline. In these cases, additional information (including magnetic resonance imaging [MRI] or computed tomography [CT] imaging if not performed before; PROPKD score >6, a family history with onset of kidney replacement therapy (KRT) <60 years in ≥2 first-line family members) should be acquired to ensure ADPKD as the primary reason for eGFR loss. ‡Because some people with Mayo Class 1C may not have rapid disease progression, we advise considering additional information, particularly in the people with age-adjusted height-adjusted total kidney volume (htTKV) close to Mayo Class 1B, to confirm the risk for rapid disease progression (e.g. evidence of eGFR decline or of a reduced age calibrated eGFR. Predicting
Renal Outcome in Polycystic Kidney Disease (PROPKD) score >6, family history with onset of KRT <60 years in ≥2 first-line family members, or novel biomarkers)

**Key information**

*Balance of benefits and harms*

Tolvaptan is an oral non-peptide vasopressin receptor antagonist that specifically inhibits binding of AVP at the V2 receptor of the collecting duct causing the selective diuresis of electrolyte-free water (also known as aquaresis).

Our systematic review found 3 RCTs, together with 2 extension studies; a pooled, matched comparison of long-term tolvaptan-treated and untreated groups; and a post-marketing analysis of harms. 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%; (95% CI: -3.3 – -2.1), both favoring tolvaptan. UTIs were less common with tolvaptan (OR 0.65; 95% CI 0.5–0.86), kidney stones and hematuria were reduced in TEMPO 3:4 trial associated with a decrease in kidney pain events (HR, 0.64; 95% CI 0.48–0.86). In one study, the risk ratio for eGFR decrease was 0.62; 95% CI: 0.38–0.98 and the HR for pain reduction was 0.64; 95% CI 0.48–0.86. An analysis of the U.S. post-marketing Risk Evaluation and Mitigation Strategy (REMS) database found that serious or potentially fatal liver events occurred in 0.06% of treated participants with no deaths or liver transplants recorded. The same study also reported a drug-induced liver injury rate of 1.57 per 100 patient-years across tolvaptan trials. In particular, one trial found that elevated transaminase levels were more common in the tolvaptan than the placebo group (5.6% vs. 1.2%). Other outcomes had imprecise estimates of effect or were not reported.

Notably, the evidence base is mainly driven by 2 multinational, pivotal RCTs (TEMPO 3:4 and REPRISE; Figure 26). In the TEMPO 3:4 trial, participants were aged between 18–50 years with TKV ≥750 ml and estimated creatinine clearance ≥60 ml/min by the Cockcroft-Gault formula. In the REPRISE trial, there were age-dependent criteria for eGFR that were used to categorize people at high-risk (18–55 years and eGFR 25–65 ml/min per 1.73 m^2; 56–65 years and 25–44 ml/min per 1.73 m^2 with prior decline in eGFR >2 ml/min per 1.73 m^2 per year).
Figure 26. Summary of TEMPO 3:4 and REPRISE trials.\textsuperscript{22, 23} ALT, alanine transaminase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; REPRISE, Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume

The results of both trials demonstrated that tolvaptan reduced kidney disease progression, in people with either early (CKD G1–G2; TEMPO 3:4) or later (CKD G2–G4; REPRISE) stages of CKD, as assessed by different primary endpoints (rate of increase in TKV and rate of decline in eGFR respectively).\textsuperscript{22, 23} However, as the goal of medical treatment is to delay onset of kidney failure, changes in eGFR have greater clinical relevance. In TEMPO 3:4, tolvaptan reduced the eGFR loss by 35% per year (−1.0 ml/min per 1.73 m\textsuperscript{2} per year from -3.70 to -2.72 ml/min per 1.73 m\textsuperscript{2}) in early-stage ADPKD (18–50 years of age with CKD G1–G2).\textsuperscript{22, 23} The results of the REPRISE study extended these findings to later stage ADPKD (defined by CKD G3–G4), where tolvaptan reduced the rate of decline in eGFR by approximately 1.27 ml/min per 1.73 m\textsuperscript{2} compared to placebo.\textsuperscript{22, 23} Subgroup analysis of the REPRISE trial showed that people between 18–55 years old benefited whereas those >55 years (n=190) had minimal benefit. With only sparse evidence from people >55 years of age, the conclusion about the use of tolvaptan in older adults is less certain.

\textit{Post hoc} analyses of the TEMPO 3:4 trial suggested that most (65\%) of the reduction in TKV occurred during the first 12 months of treatment, with limited additional chronic benefit thereafter. This might be due to different mechanisms that explain the acute and chronic effects on reducing cyst fluid secretion and cystic epithelial proliferation, respectively.\textsuperscript{313}

The use of tolvaptan in these pivotal clinical trials was associated with aquaretic adverse events due to the dose-dependent blockade of water reabsorption in the collecting duct.\textsuperscript{314} The aquaretic adverse events occurred within a median of 2 days of commencing tolvaptan and were most intolerable during the initial 3 weeks of treatment.\textsuperscript{314} Thirst (55.3\% vs. 20.5\%), polyuria (38.3\% vs. 17.2\%), and nocturia (23.2\% vs. 5.4\%) were the main aquaretic side effects. At the maximal dose (120 mg/day), the mean urine volume increased from 3–7 liter/day in people with CKD G1–G2. In people with CKD G4, the urine volume increase was slightly less at 5 liter/day.
In both pivotal trials, less than two-thirds (55%–61%) of people tolerated the highest dose of tolvaptan (120 mg/day, taken 90 mg morning + 30 mg afternoon). The aquaretic adverse events require behavioral adaptation and can be tolerated by most people, but QoL is improved when urine volume is reduced by ~25% from its peak level. Younger people with ADPKD in earlier stages of disease progression are more sensitive to aquaretic symptoms, and this should be taken into consideration when up-titrating the dose.

In TEMPO 3:4, after 3 years of therapy, 75% of tolvaptan subjects indicated that they could tolerate their current dose for the rest of their lives, compared to 85% of placebo subjects. These findings were corroborated by results in the open-label extension trial TEMPO 4:4.

Typically, the liver transaminase elevations were mild and reversible when tolvaptan was stopped, but 0.06% of people developed more serious liver injury. Tolvaptan causes a decline in eGFR during the first month of therapy (due to combination of either suppression of glomerular hyperfiltration and/or reduced kidney plasma flow, secondary to volume depletion) which stabilizes. Additional side effects include hyperuricemia (3.9% vs. 1.9%) and, rarely, gout (2.9% vs. 1.4%) compared to placebo in the TEMPO 3:4 trial. Hyperuricemia was present in 2.8% of people treated with tolvaptan in the long-term follow-up of the REPRiSe and TEMPO 3:4 cohorts. Recently, serum creatinine kinase elevation has been reported in 28% of 97 people treated with tolvaptan.

The main uncertainty regarding tolvaptan treatment is the long-term effect on reducing kidney failure (Figure 27). However, the effect of tolvaptan on the rate of eGFR decline is accepted by regulatory authorities as a reliable surrogate for delaying the onset of kidney failure. The effect of tolvaptan on rate of decline in eGFR (1.3 ml/min per 1.73 m²) is comparable to other kidney-protective agents used for other causes of CKD, such as ACEi, but could be less than others, such as SGLT2i. However, treatment with tolvaptan needs to be sustained for many years to prevent or delay kidney failure. Recent real-world data indicate that 76% of people persisted with treatment for 12 months, but long-term data are not available.

Figure 27. Schematic diagram summarizing the harms, benefits, and uncertainties regarding long-term treatment with tolvaptan in people with rapidly progressing ADPKD. Adapted with permission from Chebib et al.

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Certainty of evidence

The overall certainty of evidence was graded as moderate based primarily on the certainty of evidence for eGFR, with consistent low certainty findings for other outcomes (Supplementary Table S11). The 3 primary RCTs had no serious methodological concerns, but the summary evidence is based, in part on unblinded, observational extension studies of 2 of the trials; thus, overall, there were some methodological concerns, reducing the certainty of evidence. The critical outcome change in kidney function had moderate certainty of evidence; however, there was no evidence about kidney failure. Other critical outcomes (TKV, pain, and liver injury) had low certainty of evidence due to limited data available for meta-analysis. There were no studies or very low certainty evidence for other critical outcomes due to imprecision in effect estimates. There was moderate certainty of evidence for the important outcomes UTI, due to some methodological limitations, and serious polyuria, due to some methodological limitations and some inconsistency but large effect sizes. There was low or very low certainty of evidence for other important outcomes (serious thirst, discontinuations due to adverse events) due to imprecision and inconsistency across studies. Based primarily on the moderate certainty of evidence for eGFR, with supporting moderate and low certainty of evidence for other critical and important outcomes, we concluded that the overall certainty of evidence is moderate (Level B).

Values and preferences

There is an unmet clinical need for a treatment to prevent or slow progression of disease and reduce the risk of kidney failure due to ADPKD. There are no other proven pharmacological agents to prevent or slow disease progression. However, the benefits have to be balanced against the significant side effects of polyuria, dehydration and thirst, and the potential risk of serious liver injury (Figure 27). These safety concerns require careful patient selection, meticulous compliance with maintaining hydration, and vigilant clinical and laboratory monitoring. Thus, tolvaptan is not suitable for all people with ADPKD and selection should be based on criteria that indicate rapidly progressive kidney disease or high risk of rapid disease progression, absence of contraindications, and patients’ tolerance and adherence with monitoring. It can be expected that many people will choose to forgo tolvaptan treatment. Nevertheless, the advantages of tolvaptan in slowing disease progression outweigh the disadvantages in people who are <55 years old and meet the definition of rapid progression, as specified in Figure 24.

Resource use and costs

Tolvaptan has regulatory approval with government subsidy in many but not all countries, limiting universal accessibility. Historically the cost of tolvaptan has been very high. However, in recent years, the cost of tolvaptan has been considerably reduced and generics have entered the market in several countries around the world. Although there are regional differences in price and reimbursement regulations, prescription of tolvaptan has generally become more affordable to the person with ADPKD.

Once tolvaptan is started, it needs to be maintained until CKD G5. Although tolvaptan can slow progression, it may cause a heavy financial burden on people with ADPKD and their families. Tolvaptan treatment may interfere with a person’s work or school because of increased
urination and thirst, and monthly visits for testing, which can negatively impact a person’s finances. Some occupations are not suited to the use of tolvaptan.

Considerations for implementation

In most countries, tolvaptan has regulatory approval for people between the ages of 18–55 years of age. However, this restriction requires further validation in real-world population cohorts and registry data. Similarly, the treatment response in people with non-European backgrounds is not clear and should be investigated further, as subgroup analysis (which could be underpowered) of this subpopulation in REPRISE suggested less certain benefits (mean eGFR in non-White groups for tolvaptan vs. placebo: -3.29 ml/min per 1.73 m² vs. -3.54 ml/min per 1.73 m²; P=0.79). The long-term tolerability in young people and tools that promote adherence also require further investigation.

It is suggested that tolvaptan not be initiated with eGFR <25 ml/min per 1.73 m² as this has not been tested in RCTs and benefits are likely to be limited. In such people with low GFR, the acute drop in GFR that occurs when tolvaptan is initiated may offset any beneficial effects on the slope of eGFR loss. Furthermore, this reversible hemodynamic effect of tolvaptan also suggests that tolvaptan should be stopped in people with eGFR <15 ml/min per 1.73 m² as the small, predicted increase in eGFR may provide benefit in delaying onset of KRT. See Practice Point 4.1.1.2 regarding treatment of people >55 years old.

Rationale

The Work Group concluded that most people with ADPKD and a high risk for kidney failure would wish to be offered treatment with tolvaptan based on the available evidence. This recommendation was based on a systematic review of RCTs and their extension studies examining tolvaptan in people with ADPKD with ≥1 year follow-up. Although only 5 studies were identified, there was a high certainty of evidence that progression of kidney disease was slowed by 1.3 ml/min per 1.73 m²/year (33% relative reduction) compared to placebo. This benefit was greatest in people who were age ≤55 years and with eGFR ≥25 ml/min per 1.73 m² and established or at high risk for rapid progression. The pivotal studies reported that there was also a reduction in kidney pain and frequency of UTIs. The main risk for harm was a low risk of serious liver injury (0.06% of participants) and this risk can be reduced by surveillance monitoring of liver function tests monthly for the first 18 months and then 3-monthly life-long, as mandated by regulatory bodies. The other notable consequences of using tolvaptan long-term included aquaretic-related adverse effects, consisting of polyuria and thirst, which may be disruptive for people but are potentially adaptable and are reversible on reduction in dose or discontinuation of treatment. However, several areas of uncertainty remain. First, the pivotal studies did not include data on QoL, psychosocial effects, bulk symptoms, and extrarenal manifestations, and thus long-term tolerability and persistence with treatment are not clear. Furthermore, the beneficial impact of tolvaptan on the long-term outcome event of developing kidney failure are hypothesized but have not been validated in observational cohort studies. Given that tolvaptan is the first disease-modifying drug to slow the progression of high-risk for kidney failure, on balance the Work Group concluded that the benefits outweigh their harms and uncertainties.
The pivotal studies included adults in the pivotal trials with a diagnosis of ADPKD based on imaging criteria, as defined by the Pei-Ravine criteria (if positive family history) or >10 cysts per kidney on imaging in the absence of family history.\textsuperscript{22, 23} In the absence of a family history, the imaging criteria to fulfill the diagnosis of ADPKD are based on expert opinion, and the diagnosis should be made after other causes of cystic kidney disease have been considered (such as such as acquired age-acquired kidney cysts) and if required molecular genetic testing, if imaging is equivocal. In this regard, as in standard clinical practice, molecular genetic testing was not required to make a diagnosis of ADPKD prior to the commencement of tolvaptan in the pivotal studies. One trial has evaluated the safety and efficacy of tolvaptan for 12 months in children/adolescents with ADPKD, with insufficient power to detect significant changes in hTKV. Tolvaptan exhibited pharmacodynamic activity in pediatric ADPKD. Aquaretic effects were manageable, with few discontinuations.\textsuperscript{310} To date, no trials have examined the efficacy of tolvaptan in cystic kidney diseases other than ADPKD (i.e., ARPKD, tuberous sclerosis, HNF-1b cystic kidney disease and other rare syndromic forms) and its use is not advised in these disease categories, until further data are available.

**Practice Point 4.1.1.1:** Shared and individualized decision-making should be undertaken when deciding to initiate tolvaptan in people $>$55 years old.

Subgroup analysis of the REPRISE study in the age group $>$55 years with an eGFR $<$45 ml/min per 1.73 m$^2$ showed only a very small difference between tolvaptan and placebo in the rate of decline in eGFR (-2.54 vs. -2.34 ml/min, respectively), despite rapid progression of CKD as evidenced by a decline in eGFR $>$2 ml/min per year. With increasing age, other comorbidities (e.g., diabetes, hypertension) are likely to contribute to declines in eGFR that will not be responsive to tolvaptan. In a prospective observational cohort analysis of the ERA-European Dialysis and Transplant Association (EDTA), 20,483 people with ADPKD in 12 European countries (between the years 1991–2010) commenced KRT between 57–58 years of age, and thus most rapid progressors would have reached kidney failure by the age of 55 years.\textsuperscript{324} Therefore, the remaining people not on dialysis will likely have slowly progressive disease, and thus, will not match the indication to prescribe tolvaptan.

The analysis is limited by the small numbers (n=190 people) in this subgroup, making the definitive decisions in specific people less certain. Therefore, shared, individualized decision-making should be undertaken to balance the risks and possible benefits in people $>$55 years old with proven rapidly progressive disease.

**Practice Point 4.1.1.2:** To determine eligibility for tolvaptan treatment, rapid disease progression is defined as a confirmed annual eGFR decline $\geq$3 ml/min per 1.73 m$^2$, based on $\geq$5 measurements over a period of $\geq$5 years. Evidence for rapid disease progression is also present if a person with ADPKD has CKD G3-G5 before age 45 years, enlarged kidneys, and no other explanation for reduced kidney function.
ADPKD is a heterogenous disorder with variable long-term kidney disease prognosis with ~60% of people developing kidney failure by the age of 60 years. The pivotal trials of tolvaptan demonstrated that the rate of progression was reduced only in people with high lifetime risk for kidney failure. Therefore, defining rapid progression in people with ADPKD by historical decline in eGFR is a critical assessment for the prescription of tolvaptan. The slope of eGFR should be evaluated over a 5-year period with sufficient measurements of SCr (at least five, using IDMS traceable assays) to allow a reliable assessment of rate of decline, in order to avoid variations due to random day-to-day fluctuations in SCr and eGFR. The MIC is a practical tool to identify people at risk for rapid progression. A post hoc analysis of TEMPO 3:4 showed equal benefit from tolvaptan on kidney growth and eGFR decline in the people with Class 1C, 1D, or 1E. Because some people in Class 1C, particularly those with an age adjusted htTKV close to Class 1B, confirmatory evidence by other methods is helpful (see Figure 25).

For CKD in general, KDIGO has defined rapidly progressive decline in kidney function as ≥5 ml/min/yr. However, in people with ADPKD, a decline of eGFR of less than this value may be associated with kidney failure before the age of 58 years. In the placebo arms of the REPRISE and TEMPO 3:4 studies, which were enriched with people with rapid progression, the average annual rate of decline was approximately 3.5 ml/min per 1.73 m². In unselected cohorts of people with ADPKD, the average rate of decline was approximately 3.0 ml/min per 1.73 m², suggesting that a historic annual decline of ≥3 ml/min per 1.73 m² would be a good definition.

**Practice Point 4.1.1.3:** The Mayo Imaging classification, based on MRI, should be used as the primary imaging method for risk prediction and in consideration of tolvaptan in routine clinical care.

The historical rate of eGFR decline is a widely used marker to define risk for progression (Figure 25). However, the Mayo classification is currently the best imaging tool to define risk for progression of ADPKD and can be particularly helpful for clinical decision-making for initiation of tolvaptan during early-stage ADPKD when eGFR is preserved. Using MRI (or CT scan) cases are subdivided into typical or atypical ADPKD. TKV is measured by stereology (TKVs) or estimated by the ellipsoid equation (TKVe) using MRI in typical cases and subclassified according to age-adjusted growth rates for htTKV ranges into categories 1A–1E. Thus, subclasses 1A and 1B have slow progression of disease whereas 1C, 1D, and 1E have rapid progression. People with ADPKD subclasses 1D and 1E should be considered for treatment with tolvaptan whereas decision-making in subclass 1C should take into account additional markers of risk for progression (Figure 25). Scans should be reviewed by experienced radiologists and nephrologists to ensure correct classification. Ideally, the assessment of MIC is performed by MRI to avoid radiation exposure.

Since its development in 2015 by Irazabal et al., the MIC has been validated in a number of large cohort studies (e.g., the worldwide Observational Study in Patients With Autosomal Dominant Polycystic Kidney Disease [OVERTURE] study and the Korean KoreaN cohort study for Outcome in patients With Polycystic Kidney Disease [KNOW-PKD] cohort). The main limitations in the utility of the MIC as a tool for decision-making for
tolvaptan is the accessibility to MRI (cost and reimbursement; contraindications to MRI) and TKV stereology (although this can be overcome by use of the ellipsoid formula) and lack of long-term validation studies.

The PROPKD score provides an additional clinical framework to identify risk for progression, where either historical rate of decline in eGFR and/or MIC are equivocal. The PROPKD score was developed from a cross-sectional study 1341 participants from the Genkyst cohort and evaluated the influence of clinical and genetic factors on kidney survival. A scoring system from 0–9 was developed- being male: 1 point; hypertension before 35 years of age: 2 points; first urologic event before 35 years of age: 2 points; PKD2 mutation: 0 points; nontruncating PKD1 mutation: 2 points; and truncating PKD1 mutation: 4 points. Three risk categories were defined: low risk (0–3), intermediate risk (4–6), and high risk (7–9) for progression to kidney failure. A score >6 is an indicator of rapid disease progression and can be used in cases in which the rate of eGFR decline and/or MIC estimates are inconclusive or contradictory.

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

Tolvaptan is unlikely to impact the decline in kidney function due to other causes of CKD. Thus, it is important to rule out other causes of rapid eGFR decline in people before starting therapy. This is especially important in older people where comorbidities like diabetes, hypertension, and heart failure may be present and may cause a decline in kidney function unrelated to ADPKD. Other clues would be the presence of heavy proteinuria that may indicate another form of CKD in addition to ADPKD. Loss of kidney function in people with ADPKD tends to be linear, and a sudden decrease in eGFR may indicate superimposed AKI (e.g., due to concomitant use of nephrotoxic drugs, volume depletion or poorly controlled hypertension) (Figure 25).

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.

The relative and absolute contraindications for tolvaptan are listed in Table 6.
**Absolute**

- eGFR at initiation <25 ml/min per 1.73 m²
- Planning pregnancy, pregnancy, or breastfeeding
- Medical conditions associated with or at high risk of volume depletion
- Inability to respond or perceive thirst
- Uncorrected hypernatremia
- Urinary tract obstruction
- Strong CYP3A inhibitors*
- Significant liver disease unless due to PLD

**Relative**

- History of gout
- Moderate CYP3A inhibitors†, P-gp inhibitors‡, grapefruit juice
- Urinary incontinence

**Table 6. Checklist of contraindications to initiating and/or maintaining tolvaptan.** *e.g.*, ketoconazole, itraconazole, clarithromycin, lopinavir, ritonavir, and indinavir. †e.g., amiodarone, erythromycin, fluconazole, diltiazem, verapamil, grapefruit, imatinib, and fosamprenavir which can increase tolvaptan exposure and reduction of dose may be necessary. ‡e.g., calcium channel blockers, cyclosporin, dabigatran etexilate, digoxin, erythromycin, loperamide, protease inhibitors and tacrolimus which can increase tolvaptan exposure and reduction of dose may be necessary. ADPKD, autosomal dominant polycystic kidney disease; CYP3A, cytochrome P450, family 3, subfamily A; eGFR, estimated glomerular filtration rate; P-gp, P-glycoprotein.

As discussed under Considerations for implementation of Recommendation 4.1.1.1, the drop in eGFR upon initiating tolvaptan may hasten the onset of kidney failure in advanced CKD. There are no data of the use of tolvaptan in pregnancy and the potential risk of teratogenicity. Pregnant women or those planning pregnancy should discontinue tolvaptan. It is also best avoided in lactating women. As the major side effect of tolvaptan is aquareasis, it should be avoided if hypernatremia or hypovolemia is present or there is a predisposition to hypernatremia or hypovolemia. Because of the risk of severe liver injury with tolvaptan it should be avoided in those with significant hepatocellular liver disease unless it is due to PLD. Tolvaptan may raise uric acid slightly and should be used with caution in people with pre-existing gout.

Drug interactions are also important considerations. Concomitant use of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, lopinavir, ritonavir, and indinavir) are contraindicated. The use with moderate CYP3A inhibitors (e.g., amiodarone, erythromycin, fluconazole, diltiazem, verapamil, grapefruit, imatinib, and fosamprenavir) can increase tolvaptan exposure and reduction of dose may be necessary and grapefruit should be avoided. There is a similar caution related to P-glycoprotein inhibitors (e.g., calcium channel blockers, cyclosporin, dabigatran etexilate, digoxin, erythromycin, loperamide, protease inhibitors and tacrolimus).

Statins may be safely prescribed in ADPKD with careful attention to liver function tests (LFTs). In a post hoc analyses of the pivotal tolvaptan trials, there was no difference in statin related adverse events between tolvaptan plus statin compared to placebo plus statin groups.329
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 (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 (Figure 28).

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

The practice points list the dosage regimens for tolvaptan that have been investigated and in clinical trials of people with ADPKD which led to regulatory approval, where applicable. The asymmetric twice daily dosage delivers the likely maximal aquaretic effects during the day with the lower mid-day dosage designed to mitigate the aquaretic effect during night. Additionally, this has been the minimum effective dose investigated. People working night shifts should time their doses to match the time of day they are awake. People unable to tolerate 45/15 mg dose can be downtitrated to 30/15 mg or 15/15 mg. Although the efficacy of these reduced doses has not been tested in clinical trials, a possible benefit cannot be ruled out, particularly in people where these reduced doses are sufficient to maintain the urine continuously hypotonic.

Figure 28. Commencement and titration approach to tolvaptan in ADPKD. Examples of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (reduce clearance by >80%): antifungals (itraconazole, ketoconazole), antibiotics (clarithromycin), protease inhibitors (saquinavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, tipranavir). Examples of moderate CYP3A inhibitors (reduce clearance by 50%–80%): antiarrhythmics (amiodarone), antifungals (fluconazole), antibiotics (erythromycin), calcium channel blockers (diltiazem, verapamil), protease inhibitors (amprenavir, fosamprenavir); complementary/dietary agents: grapefruit juice (240 ml coadministration)

After successful commencement of the starting dose of tolvaptan, uptitration to 60 mg and 30 mg per day, and then further to 90 mg and 30 mg per day at a minimum of 1-week intervals should be the clinical aim. This is to achieve maximal clinical effect and the desired clinical outcomes in a manner congruent to that expected with those observed in the tolvaptan clinical trials. Monitoring through uptitration should generally be accompanied by kidney
function, blood electrolyte (sodium levels), and LFT monitoring in blood samples taken in the morning before dose of tolvaptan for most accurate assessment. Serum sodium levels may provide insight into the adequacy or excess of water intake if either hypernatremia or hyponatremia develop, respectively. Future research should investigate the time-response to dosage up titration and long-term efficacy assessment.

The goal of up titration is to achieve a sustained inhibition of AVP at the kidney V₂ receptor to maximize the effects on kidney cyst growth and kidney function decline, while allowing behavioral adaptation to the aquaretic adverse events. A thoughtful stepwise dose escalation is indicated with a close engagement between prescribing healthcare provider and patient for assessment of side effects and laboratory monitoring. Dose adjustment is not required in case of kidney function impairment. Tolvaptan therapy should continue at the highest-tolerated dose until KRT commences, unless there is an objective indication to pause, cease, or downtitrate sooner. There is some uncertainty as to whether there may be potential indications or individualized scenarios in which consideration should be given for tolvaptan cessation as a person progresses through late CKD (CKD G4–G5) prior to KRT commencement. A post hoc analysis retrospectively comparing the rate of eGFR decline in REPRISE and its open-label extension trial in people with eGFR 15–29 ml/min per 1.73 m² suggested a beneficial effect of tolvaptan in very advanced CKD. Given the sparse evidence and experience, shared decision-making is indicated to tailor patient-centered care while maximizing benefit within a scope of acceptable and minimized clinical risk.

There are no specific biomarkers that have sufficient specificity or sensitivity to verify the effectiveness of tolvaptan on disease progression. As a direct marker of the action of V₂ signaling on the kidney tubule, urine osmolality has been considered as a potentially useful marker of ADPKD progression. Post hoc analysis of TEMPO 3:4 revealed that the urine osmolality response to tolvaptan depended on baseline eGFR and urine osmolality. Among subjects receiving tolvaptan, those with a greater suppression of urine osmolality had slower kidney function decline.

Plasma copeptin, a surrogate marker of AVP, has been explored as a potential future biomarker of disease progression and tolvaptan treatment effect, though this requires clinical validation before applied routinely in clinical practice.

A close and ongoing discussion between prescribing healthcare provider and patient is critical to treatment success. This may include tailoring treatment and clinical monitoring to patient circumstances and avoiding therapeutic scenarios that either degrade clinical efficacy or increase patient risk.

4.1.4. Counseling people with ADPKD who are receiving tolvaptan
Practice Point 4.1.4.1: Physicians should be aware 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 written information about drug-drug interactions.
Practice Point 4.1.4.2: Education should be provided to people with ADPKD regarding the adverse effects of tolvaptan related to 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 aquaretic side effects to ensure long-term tolerability.

As with any therapy, the relative benefits and harms should be discussed before initiating tolvaptan. As noted above, the major benefit in appropriate people is a reduction in the rate of kidney function decline (between 25%–33%) equating to potential delay in KRT by 1 year for every 3–4 years of tolvaptan treatment in people with ADPKD. Conversely, the major potential harms include potential LFT derangement within the first 18 months of treatment and the need for kidney and liver function test monitoring monthly during that time. Owing to the mechanism of action of tolvaptan, aquaretic adverse events are anticipated to occur, including polyuria, nocturia, and excess thirst. Consideration of the potential interaction of these side effects with concomitant medical conditions and personal scenarios, such as type of work/workplace and hobbies, should be actively considered and discussed.

At present there is insufficient evidence to support any specific concomitant treatment to mitigate or minimize aquaresis, polyuria, and potential nocturia. One small study of 27 participants receiving tolvaptan suggested that 24-hour osmolar excretion was strongly correlated with 24-hour volume (b=0.73, P<0.001) suggesting that reducing dietary solute may mitigate tolvaptan-induced aquaresis. Instead, focus should be placed on discussion around medication timing and administration to manage these potential side effects. It is generally recognized that long-term tolerability of tolvaptan is likely to be maximized by open and meaningful discussion and education between a treating healthcare provider and patient.

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

Practice Point 4.1.4.4: People with ADPKD should be advised to skip doses of their tolvaptan in situations associated with risk of dehydration, such as limited access to water (including hiking or traveling), diarrhea, or vomiting, and when activities in warm weather increase insensible water loss.

People with ADPKD undergoing surgical procedures or who experience an acute medical event that predisposes to intravascular volume depletion should interrupt tolvaptan treatment. It may be advisable for people with ADPKD, their kidney healthcare provider, and primary care physician to consider a sick-day plan while being treated with tolvaptan. For instance, in case of vomiting, diarrhea, excessive sweating, and/or not being to drink, temporary interruption of tolvaptan should be implemented until clinical advice or those circumstances remit. The reasoning for this is that rapid acute complications may occur if a person continues tolvaptan while unable, either partially or fully, to replace urinary losses due to aquaresis. Tolvaptan
interruption might also be indicated when clinical monitoring cannot be undertaken, especially monthly kidney and liver function monitoring within the first 18 months of tolvaptan treatment.

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.

![Figure 29. Monitoring and management for potential hepatotoxicity in people with ADPKD on chronic treatment with tolvaptan. ALT, alanine transaminase; AST, aspartate aminotransferase; ULN, upper limit of normal.](image)

Approximately 5% of people with ADPKD treated with tolvaptan in clinical trials displayed an increase in transaminases above 3-fold the upper limit of normal (ULN). By monitoring LFTs every 3–4 months, the data from the TEMPO 3:4 and TEMPO 4:4 studies showed that alanine transaminase (ALT) increases >3-fold the ULN at least once in 4.4% of treated people versus 1% of people on placebo.22, 313 Among 1271 people treated with tolvaptan, 3 met the Hy’s law criteria (i.e., serum ALT >3 times the ULN and bilirubin >2 times the ULN), associated with a 10% risk of progression to acute and irreversible liver failure. The increases in ALT occurred most often during the first 18 months of treatment and resolved within 1–4 months after tolvaptan cessation.334, 335 Based on these data, in the REPRISE trial, LFTs were
monitored on a monthly basis. In this study, ALT increases >3 times the ULN occurred in 5.6% of people treated and 1.2% of people on placebo. However, likely due to this more frequent monitoring and consequent earlier discontinuation of tolvaptan, no one met the Hy’s law criteria in this study. A recent study showed that among 38 people rechallenged with tolvaptan after the initial drug-induced liver injury episode, 30 displayed return of increased liver enzyme levels. This study identified a signature pattern of susceptibility to tolvaptan hepatotoxicity, which includes onset of hepatocellular injury usually between 3 and 18 months of starting the drug and injury gradually resolving over 1–4 months following discontinuation of tolvaptan. The absence of Hy’s law cases in REPRISE and the long-term extension trial corroborated the recommendation of liver enzyme monitoring during the first 18 months of tolvaptan and every 3 months thereafter to detect and manage increases in liver enzyme levels.

The mechanism of this potential hepatotoxicity is largely unknown, likely idiosyncratic. This elevation is usually reversible upon discontinuation of tolvaptan. Based on the rare severe cases that fulfilled the Hy’s law criteria, a risk management plan was implemented, requiring close monitoring of hepatic transaminases, total bilirubin, and alkaline phosphatase. It is therefore mandatory that people treated with tolvaptan receive LFTs prior to starting the treatment and monthly for 18 months (biweekly in the first month) and every 3 months thereafter. This recommendation was based on the previously mentioned data that almost all cases of liver abnormalities triggered by tolvaptan occurred within the first 18 months and that the implementation of the proposed monitoring process in the REPRISE trial was associated with no more cases fulfilling the Hy’s law criteria.

All physicians prescribing tolvaptan for ADPKD in the U.S. must be trained and certified to appropriately apply the REMS program, while the European Medicines Agency (EMA) has implemented a risk management plan that includes education of both prescribing physicians and people with ADPKD. Tolvaptan should be immediately withheld at the onset of signs or symptoms consistent with hepatic injury or if ALT, aspartate aminotransferase (AST), or bilirubin levels increase above 2-fold the ULN. If these levels have not reached 3-fold the ULN, ALT, AST, alkaline phosphatase, and total bilirubin should be repeated within 48–72 hours to confirm the levels and establish whether they present increasing or decreasing trends. In the setting of increased levels of liver enzymes, the physician should investigate concurrent diseases, drug use, alcohol use, recreational drug use, changed or special diets, exposure to chemical agents, and excessive exercise. Acute viral hepatitis, autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic liver injury, and biliary tract diseases should also be ruled out. If the LFTs remain abnormal following discontinuation of tolvaptan, the person should be referred to a hepatologist. If they resolve, tolvaptan may be reinitiated, however with increased frequency of monitoring (weekly for the first month) provided that ALT, AST, and bilirubin remain below 3-fold the ULN. Tolvaptan should not be reinitiated in the settings of signs or symptoms consistent with hepatic injury or of ALT, AST, or bilirubin levels that reached values ≥3 times the ULN at any point of the treatment, unless such conditions were linked to other etiologies and have resolved. While these guidelines for permanent discontinuation of tolvaptan are applied in the U.S., they are not uniform among countries. In that regard, the criteria recommended for definitive cessation of tolvaptan by the EMA and
Health Canada's Health Products and Food Branch (HPFB) are any of the following: 1) ALT or AST >8-fold the ULN; 2) ALT or AST >5-fold the ULN for more than 2 weeks; 3) ALT or AST >3-fold the ULN and (total bilirubin >2-fold the ULN or International Normalised Ratio [INR] >1.5); or 4) ALT or AST >3-fold the ULN with persistent symptoms of hepatic injury. All people who discontinued tolvaptan due to hepatotoxicity should be followed until laboratory and clinical resolution.

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: Treatment with tolvaptan can be maintained until people with ADPKD approach the need of KRT initiation. Discontinuation may slightly increase eGFR.

Practice Point 4.1.6.4: People with ADPKD should be counselled regarding measures that can decrease polyuria during treatment with tolvaptan, including lowering dietary sodium and moderate reduction of dietary protein. Until further studies are available, concomitant medications should not be used to mitigate tolvaptan-induced aquaresis.

Prior to initiating the treatment, people with ADPKD should be informed that aquaretic adverse events are associated with the very mode of action of tolvaptan. In fact, polyuria is expected to occur in almost all people treated with this drug, more often exceeding 5 l/d, with frequent nocturia. It must be noted that the increase in urine volume is expected to be higher in younger people with higher GFR.331, 337 Initiating the treatment on a weekend or on a non-working day is good advice to help the adjustment to the aquaretic response. Indeed, the aquaretic effect becomes more tolerable along the following days and weeks. People should be instructed to significantly increase the ingestion of fluids to appropriately reach the ideal amount for each specific case. The ideal source of fluid is water while fluids high in sugar or fat should be avoided. Water intake should be made in anticipation of thirst or at the first sign of thirst and should include additional hydration before bedtime and fluid replenishment after each episode of nocturia.321 People should be instructed to monitor their body weight regularly as a potential indicator of dehydration.

Although nocturia may limit tolerability, most people included in studies have tolerated this side effect of tolvaptan.314, 338 Individual adjustments to the treatment may include adapting the schedule, timing, and doses of tolvaptan to the person’s activities.

If polyuria severely affects a person’s tolerance to tolvaptan, additional actions may be initiated.147, 321 Lowering dietary sodium may reduce the urine output by decreasing the excreted load of osmotically active solutes.300 It must be noted that a low-sodium diet may also have a beneficial effect on kidney disease progression and facilitate BP control.120, 121 To appropriately
monitor this advice, sodium intake can be sequentially quantified using 24-hour urine collections. Moderate reduction in protein ingestion may also contribute to reduce aquaresis.\textsuperscript{300} If nocturia remains a limiting effect, reducing the later dose may be an alternative, despite a potential reduction in V\textsubscript{2} receptor blockade efficiency.

The use of tolvaptan, a V\textsubscript{2} receptor antagonist, causes nephrogenic diabetes insipidus (NDI) resulting as a side effect in substantial polyuria.\textsuperscript{339} The diuretic hydrochlorothiazide, in turn, is an established therapy for NDI, being able to decrease urine output by around 30\%.\textsuperscript{340} In addition, metformin has been shown to decrease urine output by almost 50\% in tolvaptan-treated rats.\textsuperscript{341} In this scenario, it has been suggested that either thiazide diuretics and/or metformin could be potential concomitant treatments to mitigate tolvaptan-induced aquaresis in people with ADPKD.\textsuperscript{315} This hypothesis was supported by 2 small crossover trials of people treated with tolvaptan where short-term treatment with thiazide diuretics (trichloromethiazide, hydrochlorothiazide) or metformin reduced 24-hour urine volume by 21\%–25\% and improved QoL.\textsuperscript{315, 316} However, the long-term effect of these interventions that could potentially influence tolvaptan-induced kidney protection in people with ADPKD is not known. A planned trial will evaluate this question (NCT05373264). Currently, we advise against using a thiazide diuretic or other concomitant medication to mitigate tolvaptan-induced aquaresis.

**Research recommendations**

- Studies are needed to evaluate the time-response to tolvaptan titration.
- Long-term efficacy studies of tolvaptan are needed.
- Studies are needed to compare treating to maximally tolerated dose versus dose needed to maintain urine hypotonicity versus a fixed split low dose and high water intake prescription.
- Studies assessing the factors driving the response to tolvaptan are needed.
- Studies are needed to assess strategies to reduce polyuria during tolvaptan.
- Studies are needed to assess biomarkers of progression of ADPKD.

**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 liters of urine per day in people with ADPKD and an eGFR $\geq$30 ml/min per 1.73 m\textsuperscript{2} without contraindications to excreting a solute load (2D).

**Practice Point 4.2.1.2:** People with ADPKD should be provided specific advice and education on how much water to drink daily, how to achieve this, what fluids to drink, and how to determine if they are drinking sufficient quantities of water.

*This recommendation is based primarily on the theoretical inferences about the effect of chronic underhydration and elevated AVP levels on kidney cyst growth, as empirical evidence to support the effectiveness of increasing water intake to reduce kidney disease progression is limited. The*
recommendation takes into consideration the potential benefits of providing specific advice for habitual total fluid intake, the low risk of long-term harm, and overcoming the barriers to enable people with ADPKD to implement the intervention in the real-world.

Key information
Balance of benefits and harms

The Work Group defined increased or high water intake as habitual water intake to achieve at least 2 liters of urine per day in people with ADPKD and an eGFR ≥30 ml/min per 1.73 m² who do not have contraindications (Table 7). Maintaining adequate water intake and hydration status suppresses the posterior pituitary release of AVP. As discussed, an early elevation of AVP is an important driver of kidney cyst growth. Thus, in ADPKD, the goal of increased water intake is to suppress the release of AVP in order to reduce kidney cyst growth. As serum AVP is impractical to measure on a regular basis, urine osmolality and volume are the prime indicators to assess the effectiveness of increased water intake. Basal circulating AVP typically ranges between 0.5–2 pg/ml which results in a urine osmolality that is ~1–2-fold higher than serum osmolality and urine volume between 1–3 liter/day. In ADPKD, as the release of AVP is increased by 1.5-fold, in part due to collecting duct resistance from local kidney cyst formation, urine production is therefore decreased. The maximal suppression of AVP below 0.5 pg/ml will produce urine volume >3 liter/day but requires fluid consumption that exceeds population-based recommendations (>8 liter/day) and increasing risk for life-threatening hyponatremia.

Overall, the empirical evidence to support the effectiveness of increasing water intake to reduce kidney disease progression is limited. Long-term data include a single 3-year multicenter study that compared the effect of usual ad libitum water intake versus individualized, prescribed, and closely monitored water intake to reduce urine osmolality to ≤270 mOsmol/kg. The mean 24-hour volume was 3 liter/day in the intervention group and 2.5 liter/day in the control arm. The study found no significant differences between groups on the rate of hTKV, eGFR decline, systolic and diastolic BP, and pain.

In the judgement of the Work Group, there are minimal risks associated with increased water intake to produce a urine output of between 2–3 liter/day in people with an eGFR ≥30 ml/min per 1.73 m² and without contraindications to excreting a solute load (Table 7). In large studies, most people with ADPKD had a mean urine volume of 2.4 liter/day at baseline. Furthermore, in the El Damanahri et al. study and the Prevent Kidney Failure due to Autosomal Dominant Polycystic Kidney Disease [PREVENT-ADPKD] trial, increasing water intake in people with eGFR ≥30 ml/min per1.73 m², approximately 10% of people developed mild reversible hyponatremia, and not of clinical significance. In addition, adverse events and average withdrawals from the PREVENT-ADPKD study were similar between the increased fluid intake and usual fluid intake group.
Baseline hyponatremia (<135 mmol/l)
Potential safety risk for increased water intake
- Risk of fluid overload (heart failure, cirrhosis)
- Requirement for fluid restriction
Use of medications that may increase the risk of hyponatremia (SSRIs, TCAs), thiazides used for BP control

Table 7. Relative contraindications for increasing water intake. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants

The target 24-hour urine osmolality was achieved in only half of the people in the prescribed water group, while it was unexpectedly achieved by 17% of the people in the ad libitum water group. Furthermore, serum copeptin levels were not different in the 2 groups. Barriers to sustain increased water intake over a prolonged period in the trial may have limited potential benefits. It is likely that most people will need additional strategies to remind them to drink increased volumes, even when they are not thirsty (such as a smart water bottle or other reminders).  

Qualitative studies have revealed that there is a strong interest in water intake amongst people with ADPKD and specifically requested information about how much to drink. Generic statements, such as “drink plenty of water”, may be misunderstood by some people with ADPKD. In particular, water intake that vastly exceeds population-based recommendations can lead to life-threatening hyponatremia. In a systematic review of 590 people without ADPKD with life-threatening hyponatremia, psychogenic polydipsia, and iatrogenic advice were identified as underlying factors in 68% of cases. In clinical trials, specific water individualized prescriptions were developed using the free water clearance formula. However, this is not recommended for routine clinical practice, as repeated 24-hour urine collections are cumbersome for people with ADPKD; urine volumes vary from day-to-day and may be incomplete; and the cost-effectiveness compared to simply providing education at an outpatient visit has not been evaluated. People who are unable to maintain an increased water intake should be encouraged to avoid becoming thirsty.

Plain drinking water, mainly obtained from tap water, is the preferred fluid for drinking in people with ADPKD. The consumption of drinks with added sugar and/or salt (e.g. soft drinks, cordials, fruit drinks, vitamin water, energy and sports drinks) or alcohol should be minimized as these increase the risk of weight gain. While caffeine has been shown to stimulate cyst growth in vitro, longitudinal data from 2 large cohort studies (HALT and Swiss ADPKD cohort) showed that there were no differences in kidney disease progression (TKV or eGFR) between coffee and non-coffee drinkers.

A high dietary solute load (due to high salt and protein intakes) requires a higher fluid intake to maintain dilute urine. Therefore, people with ADPKD should be educated about the importance of dietary solute intake in determining obligatory urine volume (i.e., the minimal amount of urine required to excrete the daily solute load). As outlined in Chapter 7, people
with ADPKD should be advised to achieve and maintain a moderate protein intake (0.8–1.0 g/kg/d, as per WHO recommendations) and limit sodium (Na) intake (Na <2 g/d [<90 mmol/d] or <5 g salt/d).

**Certainty of evidence**

The overall certainty of evidence was graded as very low primarily due to sparseness of evidence from only a single long-term trial (Supplementary Table S12). The study had no serious methodological limitations. The study reported on the critical outcome for this comparison (CKD progression) and the important outcomes of pain, TKV, hyponatremia, and discontinuation due to adverse events, but not on QoL or psychosocial outcomes. Due to sparse evidence, we have concluded that the overall certainty of evidence is very low (Level D).

**Values and preferences**

The Work Group placed a high value on the potential benefit of slowing progression and low risk for harm and low value on the potential inconvenience from increasing water intake. In addition, high water intake prevents kidney stones, for which all people with ADPKD are at higher risk than the general population. Water intake is a regular requirement in daily life together with the wide availability, simplicity, low-cost, and safety profile of the intervention. There is no evidence that the source of water (tap, bottled, filtered) is important to the progression of kidney cyst growth. In addition, the Work Group noted the strong patient interest in increased water intake as a therapy for ADPKD. Previous self-reported estimates show that most people (61%) with ADPKD probably have a high habitual intake of fluid (≥2 liter/day) which has been induced by their healthcare providers due to previous influential publications regarding the potential benefits.\(^{199,344}\) Furthermore, the Work Group placed a higher value on the importance of specifying an approximate fluid target given that people with ADPKD have requested more specific information detail to dispel confusion and uncertainty within the community.

**Resource use and costs**

Additional costs to implement this recommendation are minimal. However, participants in the intervention group in PREVENT-ADPKD study and other studies were provided with additional resources, which could be expensive to implement (e.g., dietetic coaching, text messaging, self-monitoring of urine specific gravity).\(^{351}\) However, as most people with ADPKD in clinical trials at baseline were defined as higher water drinkers, the Work Group concluded that there is no evidence at present that these additional resources are required.

**Considerations for implementation**

The implementation of the intervention from PREVENT-ADPKD included intensive resources (dietitian, self-monitoring of urine specific gravity, text messaging). However, implementation could entail simply providing people with ADPKD with guidance on suggested water intake. Despite this, the increase in urine volume in the 3 studies was ~0.8 liter/day which declined with the longer duration of the study.
Rationale

Given the limitations of current evidence as well as the challenges in conducting future clinical trials that involve increased water intake, the Work Group concluded that people with ADPKD should be advised to maintain optimal hydration to minimize the adverse effects of AVP. This conclusion was also based on priorities specified by people with ADPKD and to minimize confusion among patients and healthcare providers, in addition to the wide accessibility and low risk associated with increased water intake. The Work Group specified urine output to define increased water intake to simplify inter- and intraindividual variability in daily fluid requirements based on insensible losses due to differences in physical activity, climate, and/or clothing.

The Work Group considered that ADPKD is a chronic disease in which dehydration should be avoided. The recommendations for fluid intake target are consistent with adequate intake target advised for the general population to prevent consequences associated with dehydration (2.6 liter/day for adult males and 2.1 liter/day for adult females). Of note, only 22% of general population reach these targets. Moreover, the recommendation is also consistent with the target specified by the American Urological Association Clinical Practice Guidelines for the prevention of kidney stones.

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 dilution hyponatremia prior to advising people with ADPKD to increase water intake.

Increased water intake should only be advised to people with ADPKD who can safely excrete the load. Therefore, prior to advising people with ADPKD to increase water intake, a brief clinical assessment integrated with routine clinical, considering current active medical problems, medical history, physical examination findings, and laboratory investigations should be performed to identify risk for fluid retention and/or life-threatening hyponatremia (Table 8). Trials have excluded people with comorbidities or risk factors for fluid retention and/or hyponatremia, including regular use of pharmacological agents that reduce the kidney capacity to excrete free water, and therefore increase risk for fluid retention (hypertension, weight gain) and life-threatening hyponatremia. The long-term use of diuretics and NSAIDs are commonly associated with hyponatremia (risk frequency between 1/100 and 1/1000) whereas other drug classes (antidepressants, antipsychotics, anti-epileptics, opioids) are rare (risk frequency 1/10,000). The risks and benefits for people with ADPKD are unclear.

Clinical trials of increased water intake in people with ADPKD excluded those planning or currently pregnant or breastfeeding due to factors that may impede completion of study procedures and/or interpretation of the primary endpoint. However, in clinical practice, neither pregnancy nor lactation is a contraindication to advising people to increase water intake, as the volumes recommended are the same for the healthy general population.
History

Comorbidities: Any medical conditions that have requirement for fluid restriction, including heart failure, chronic liver disease, nephrotic syndrome, chronic hyponatremia

Voiding mechanism: Can the voiding mechanism handle increased urine output of between 2–3 liter/day?

Diet: Does the patient consume an ultra-low sodium/protein diet (<60 mEq/d or <0.6 g/kg ideal body weight/d)?

Medications: Does the patient regularly use medications that enhance salt excretion (e.g., diuretics) or AVP production (e.g., serotonin uptake inhibitors, tricyclic antidepressants)?

Examination: Is there any evidence of fluid overload (e.g., edema)?

Investigations

Does the patient have eGFR <30 ml/min per 1.73 m²?

Does the patient have baseline hyponatremia (<135 mmol/l)?

Table 8. Factors to be considered before advising increased water intake. AVP, arginine vasopressin; eGFR, estimated glomerular filtration rate

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.

Water intake beyond drinking to thirst is not advised for people with CKD G4-G5, as there are limited safety data in this population. One short-term trial that included people with an eGFR >20 ml/min per 1.73 m² had 2 cases of reversible hyponatremia (Na <132 mmol/l, eGFR of participants was 28 and 57 ml/min per 1.73 m² respectively) among 42 participants. People with ADPKD should be assessed by the treating nephrologist for clinical contraindications. In the PREVENT-ADPKD RCT, participants who had a risk for developing hyponatremia, fluid overload and/or urinary tract obstruction were excluded from the study. These conditions may include people with a baseline serum sodium <135 mmol/l; requirement for medications that have a high-risk of precipitating hyponatremia, such as chronic use of diuretics; medical conditions that require fluid restriction, such as heart failure, chronic liver disease, nephrotic syndrome, or generalized edema; abnormalities in the voiding mechanism.

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.

Estimating habitual daily fluid intake at baseline can verify if current fluid intake is optimal and assist with subsequent education. There is no consensus on which methods should be used to estimate daily fluid intake in people with ADPKD. Multiple methods are reported, with distinct convenience to the person with ADPKD, degree of resource utilization, and accuracy. Dietary recall (such as asking the number of cups of fluid and types of fluid consumed per day) takes <5 minutes to obtain and is a simple screen to estimate fluid intake, but it is self-reported and subject to under- or over-reporting. Self-administered semiquantitative
beverage food frequency questionnaires, such as the Beverage Frequency Questionnaire (BFQ: validated in people with ADPKD), provides a structured approach and may increase patient self-awareness, but they are also self-reported.\textsuperscript{356} Measurement of 24-hour urine volume and osmolality provide the best method of estimating fluid intake and osmotic load but has some disadvantages, such as day-to-day variability in fluid intake, errors due to incomplete collections, and inconvenience to people with ADPKD.

While a daily water intake of approximately $\geq 2$ liter/day is recommended for people with ADPKD in view of the kidney-protective benefits, the effects of high water intake on liver cyst progression remain to be investigated.

**Research recommendations**

There is only one RCT that has evaluated the long-term efficacy of increasing water intake on the progression of ADPKD and further studies are needed such as:

- Short-term clinical trials to assess the efficacy of adjunctive tools to facilitate behavioral change to increasing water intake (e.g., smartphone app, smart water bottles),
- Retrospective and prospective studies of ADPKD to evaluate the level of water intake as a risk factor for progression,
- Interventional RCTs evaluating the combination of tolvaptan and water intake.

**4.3. Mammalian target of rapamycin 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).

*This recommendation places a high value on the outcomes of 4 RCTs demonstrating that the chronic use of mTOR inhibitors (everolimus, sirolimus) was associated with significant adverse effects and did not slow the rate of eGFR decline.\textsuperscript{357-360}*

**Key information**

**Balance of benefits and harms**

Four long-term clinical trials have been conducted to investigate the efficacy of mTOR inhibitors on kidney disease progression in people with ADPKD. The largest study, reported by Walz et al. was a 2-year double-blind multicenter trial undertaken in 3 countries in which 433 people with ADPKD were randomized to either placebo or everolimus (2.5 mg twice per day).\textsuperscript{360} In support of the primary hypothesis, the primary outcome, change in MRI-measured TKV at 1 and 2 years, declined in the everolimus arm at 1 year but was not significant at 2 years. The adjusted annual decline in eGFR was significantly faster in the everolimus vs. placebo (-5.5 ml/min/year vs. -3.5 ml/min/year respectively; $P<0.001$).\textsuperscript{360} Other secondary endpoints (proteinuria and BP) were similar in both arms.\textsuperscript{360} However, all-cause death (OR: 2.04; 95% CI: 0.18–22.67), doubling of SCr or kidney failure (OR: 5.26; 95% CI: 0.24–117) and discontinuation due to adverse events (OR: 3.35; 95% CI: 1.83–6.14) increased in the everolimus group.\textsuperscript{360}
The second largest study by Serra et al. was an 18-month open-label trial in which 100 participants were randomized to either sirolimus (2 mg/day) or standard care.\textsuperscript{358} Contrary to the main hypothesis, the primary outcome (change in TKV at 18 months) was not different between the 2 arms. In addition, the rate of decline in eGFR was similar in both arms, but pulmonary or upper respiratory events (OR: 5.5; 95% CI: 1.46–20.74) and cough (OR: 4.42; 95% CI: 1.15–16.97) were increased in the sirolimus arm compared to standard care.

Stallone et al. examined the role of mTOR inhibitor dose and combination with an ACEi in a prospective 2-year open-label trial in which 55 people with a P\textit{K}D\textit{I} mutation were randomized to either high-dose sirolimus plus ramipril, low-dose sirolimus plus ramipril, or ramipril alone.\textsuperscript{359} The downstream target of mTOR activation, p70S6 kinase phosphorylation, was reduced in peripheral blood mononuclear cells in the sirolimus group. However, there was no significant change in kidney function decline.

Finally, Ruggenenti et al. investigated the efficacy of mTOR inhibition in a prospective 2-year open-label trial of 41 people with ADPKD with severely abnormal kidney function were randomized to either sirolimus (3 mg/d, trough 5–10 ng/ml) or conventional treatment.\textsuperscript{357} There was no difference in TKV or GFR decline between the 2 arms. Moreover, the trial was terminated at 1 year due to adverse events (e.g., worsening proteinuria, aphthous stomatitis, acne, respiratory events) and kidney events (doubling of SCr or kidney failure, OR: 5.26; 95% CI: 0.24–117) in the sirolimus arm.

Three studies were open-label and only one was double-blind but overall, there was low-moderate risk of bias. The forest plot analysis of the 4 trials demonstrated no net benefit of mTOR inhibitor treatment on the progression of TKV and was associated with a trend for worsening GFR (estimate: -0.6; 95% CI: -3.9–2.6, P<0.1). In addition, although the certainty of evidence was low, there were sparse but strong associations with risk of harm due to adverse events across all 4 studies. An updated meta-analysis consisting of 9 RCTs and 784 people with ADPKD also concluded that mTOR inhibitors did not reduce kidney disease progression and were associated with an increased risk for adverse effects, particularly aphthous stomatitis (OR: 15.45; 95% CI 9.68–24.66) and peripheral edema (OR: 3.49; 95% CI 1.31–9.27).\textsuperscript{361}

\textit{Certainty of evidence}

The overall certainty of evidence was graded as low primarily due to some inconsistency in effect estimates across studies and sparse estimates of harms (Supplementary Table S13). The trials mostly had no serious methodological concerns, except that one trial poorly reported their study methods. The critical outcomes CKD progression and TKV progression were most commonly reported, but there was large heterogeneity of treatment effects for both outcomes across studies (with point estimates favoring either mTOR inhibitors or placebo in different studies). The summary effect estimate for TKV progression was also imprecise. Two critical outcomes (proteinuria and death) were sparsely reported, providing very low certainty of effect. Other critical outcomes were not reported. Only a single study reported individual harms due to adverse events serious adverse events, and pulmonary adverse events leading to discontinuation of therapy. Although, the effect estimates were large (OR >~2), we, therefore, concluded there
was low certainty of evidence for these outcomes. Other important outcomes were not reported. Thus, based primarily on the low certainty of evidence for CKD, TKV progression and adverse events, we concluded that the overall certainty of evidence is low (Level C).

**Values and preferences**

Based on the results of the 4 key studies, this recommendation is strong because there is evidence of potential harm. The Work Group judged that all or nearly all well-informed people would choose not to receive mTOR inhibitors given evidence of significant adverse effects without evidence that mTOR inhibitors reduce the decline in eGFR.

**Resource use and cost**

The Work Group concluded that that the lack of overall benefit and significant risk of harm was consistent in all studies and would likely lead to increased resource utilization due to the latter, irrespective of cost. Therefore, there is no justification for treating people with ADPKD at risk of rapid progression with mTOR inhibitors, either routinely or as rescue therapy in selected settings.

**Considerations for implementation**

The clinical trials regarding mTOR inhibitors were conducted in people with European ancestry but there is no evidence to suggest that the conclusions would be different in other regions of the world based on pharmacokinetic data.362

**Rationale**

Although preclinical studies in small animal models of PKD using high-doses demonstrated that mTOR inhibitors suppress the proliferation of cystic epithelial cells and reduce kidney cyst growth,363 all 4 RCTs using conventional clinical dosing demonstrated no beneficial effects on primary endpoints of kidney disease progression. Moreover, the studies found significant increases in adverse events, including risk of declining kidney function and pulmonary events, thereby excluding the use mTOR inhibitors to reduce kidney disease progression in people with ADPKD.

**Research recommendations**

- Due to the lack of tolerability of currently available agents, the development of novel mTOR inhibitors that preferentially target the kidney and/or cystic epithelium to mitigate systemic toxicity and evaluation in clinical trials is needed.

**4.4. Statins**

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

*Although statins are indicated for the treatment of hypercholesterolemia to reduce the risk of CVD (as in the general and CKD populations not receiving dialysis; see KDIGO Clinical*
there is currently no evidence that they slow the progression of kidney disease due to ADPKD.

**Key information**

**Balance of benefits and harms**

Two clinical trials have investigated the efficacy of statins in slowing disease progression, one in adults and one in children.\textsuperscript{364, 365} The trial in adults (with 49 analyzed participants) found no significant difference in eGFR between pravastatin and no treatment groups (net difference: −0.08; 95% CI: -0.71 – 0.56) at 2 year follow-up.\textsuperscript{365} However, the trial was open-label, had large loss to follow-up, and did not report an intention-to-treat analysis. The trial of 110 children randomized to either a combination of lisinopril plus pravastatin (20–40 mg/d) or lisinopril plus placebo.\textsuperscript{364} The primary outcome measure (rate of change in hTKV) was reduced in the lisinopril plus pravastatin group compared to the lisinopril plus placebo group (net difference: -9%; 95% CI: -16% – -2).\textsuperscript{364} No participant discontinued treatment due to adverse events. Overall, based on limited evidence of 2 trials, there was no high-quality evidence that statins reduce the decline in eGFR in adults with ADPKD.

Non-trial data (not systematically reviewed) included a post hoc analysis of the HALT-PKD trials that developed a propensity score model to compare statin (n=85) or no treatment (n=438) use.\textsuperscript{366} Overall, there were no beneficial effects of statins to reduce TKV or decline in eGFR.\textsuperscript{366}

**Certainty of evidence**

The overall certainty of evidence was graded as very low (Level D) for adults primarily due to there being only a single trial with serious limitations in adults (Supplementary Table S14). The overall certainty of evidence was graded as low (Level C) for children, due to a significant effect found for a critical outcome in a single trial without serious limitations. The adult trial reported only the critical outcome of change in eGFR. The pediatric study had low certainty of evidence for the critical outcome change in TKV, but insufficient evidence regarding possible harms. Most prioritized outcomes were not reported by either study.

**Values and preferences**

Statins are widely prescribed for the treatment of hypercholesterolemia and their adverse events have been extensively evaluated in the general population. However, due to limited data and the overall uncertainty in their efficacy on specifically slowing kidney disease progression in people with ADPKD, the Work Group concluded that most people would not wish to take an additional pharmacological agent for which benefits have not been established.

**Resource use and cost**

Statins are universally utilized for cardiovascular risk prevention and this is the prime rationale for its indication in people with ADPKD. Although statins are widely available and low in costs, currently there is insufficient evidence to support the routine use of statins to specifically to slow the progression of kidney disease due to ADPKD, in people for whom there are no CVD preventative benefits.
Considerations for implementation

The effectiveness of statins on slowing kidney disease progression in ADPKD is not known and well-powered, multicenter, clinical data would be required to resolve this question. Due to the limited evidence, other clinical practice guidelines in ADPKD are consistent with recommendations made by the KDIGO Work Group.367,368

Rationale

The evidence to support the use of statins to slow kidney disease progression in people is limited to 2 clinical trials both of which did not demonstrate a benefit on reducing eGFR decline. A 2-year randomized, double-blind placebo-controlled, parallel study (n=200, eGFR ≥60 ml/min per 1.73 m²; NCT03273413) is currently in progress and will provide further evidence regarding the efficacy of statins in slowing TKV.

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).

Mutations in PKD genes (PKD1, PKD2) lead to abnormalities in intracellular signaling pathways that include the downregulation of AMP-activation protein kinase (AMPK). The antidiabetic drug metformin has pleiotropic actions that include the activation of AMPK, which is hypothesized to reduce kidney cyst growth. Despite preclinical data, current evidence does not support the use of metformin to slow kidney disease progression in ADPKD.

Key information

Balance of benefits and harms

Three small clinical trials regarding the role of metformin in people with ADPKD were reported in 2021.369-372 Brosnahan et al. reported a 12-month prospective double-blind trial of 51 participants who were randomized to either metformin (500–1000 mg twice daily) or placebo.369 Eighty-two percent and 100% of participants tolerated (primary endpoint) metformin and placebo, respectively, after 12 months, and there were no differences in the secondary endpoints (change in TKV or eGFR). Adverse events in the metformin group were increased compared to placebo (OR: 4.11; 95% CI: 1.27–13.36). Mild hypoglycemia was similar in both arms (OR: 0.96; 95% CI: 0.06–16.23) and there were no episodes of lactic acidosis. Similarly, Perrone et al. reported the results of 2-year double-blind RCT of 97 people with ADPKD allocated to either metformin (500–1000 mg twice daily) or placebo for 26 months.370 The primary endpoint was tolerability of study drug, and overall, 89% receiving metformin and 81% receiving placebo met adherence threshold of >50%, and no intergroup differences for eGFR decline and TKV increase. Finally, Chaudhary et al. reported an open label trial of 70 people with ADPKD randomized to either metformin (0.5–1g twice daily) or placebo over 12 months.372 The primary outcome (percent change in TKV) was reduced in the metformin group compared to the placebo group (net difference: -0.90%; P=0.001) at 12 months. This was associated with improvements
in secondary kidney outcome measures including eGFR decline and proteinuria reduction, but minimal details were reported to assess adverse events.

**Certainty of evidence**

The overall certainty of evidence was graded as moderate based on high and moderate certainty of evidence regarding CKD and TKV outcomes, and low certainty of evidence for an increase in diarrhea (Supplementary Table S15). The 3 eligible trials had no serious methodological concerns, although one was open-label. The critical outcome CKD progression had high certainty evidence, without serious concerns about the evidence. The critical outcome TKV progression had moderate certainty of evidence due to some inconsistency across studies. Evidence for other critical outcomes were sparse (and for pain imprecise) or not reported. One study provided low certainty of evidence for risk of diarrhea, with a large effect size. Other important outcomes were sparse and imprecise, or not reported. Based primarily on the high and moderate certainty of evidence for the critical outcomes CKD and TKV progression, together with the low certainty of evidence for diarrhea, we concluded that the overall certainty of evidence is moderate (Level B).

**Values and preferences**

Metformin has a favorable safety profile that is validated by over 50 years of clinical use for other chronic conditions. This suggests that long-term clinical trials in people with ADPKD may be safely conducted to determine if metformin slows progression of kidney disease.

**Resource use and cost**

As a repurposed drug, metformin has wide availability, low-cost, and access, and this has considerable potential for the management of ADPKD.

**Considerations for implementation**

In the absence of definitive trial data, the Work Group concluded that metformin usage in people with ADPKD should be restricted to high-quality and well-powered clinical trials (such as Implementation of Metformin theraPy to Ease Decline of Kidney Function in Polycystic Kidney Disease [IMPEDE-PKD], NCT04939935) that are presently underway.

**Rationale**

Metformin is a commonly prescribed oral hypoglycemic agent that has multiple molecular actions, including the activation of AMPK. Current evidence for metformin in people with ADPKD is limited to the results of 3 small clinical trials that, except for 1 study, have primarily evaluated the safety and tolerability over 1–2 years. These data showed that, in general, metformin was well-tolerated with mild adverse events, primarily affecting the gastrointestinal system (e.g., diarrhea). Except for one preliminary study published only in abstract form, there has been no demonstrable effect on eGFR decline and/or change in kidney volume. All studies were underpowered and not designed to test the kidney-protective efficacy of metformin in people with ADPKD. Thus, long-term, well-powered RCTs are needed before the role of metformin in the management of slowing kidney disease progression can be determined.
Research recommendation

- A long-term RCT comparing metformin to placebo in people with ADPKD and CKD G2–G4 is needed.

4.6. Somatostatin analogues

Recommendation 4.6.1: We suggest that somatostatin analogues should be prescribed only 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 (2B).

Somatostatin is an endogenous hormone produced in multiple cell types (nervous system, gastrointestinal tract, kidney proximal tubular and mesangial) that suppresses intracellular cyclic adenosine monophosphate (cAMP) synthesis, and has therefore been hypothesized that may reduce kidney cyst growth. The short half-life of endogenous somatostatin has led to repurposing of somatostatin analogues (octreotide, lanreotide, pasireotide) for evaluation in ADPKD clinical trials. However, current trials have found an effect on TKV progression, but not eGFR progression, with increased risks of various side effects. Given the reduction in TKV progression, there may be a place for these drugs in the treatment of people with severe complaints related to massively enlarged kidneys. However, this group of people has not been analyzed in trials.

Key information

Balance of benefits and harms

Several clinical studies investigating somatostatin analogues reported conflicting results in people with ADPKD. For instance, the Somatostatin In Patients With Autosomal Dominant Polycystic Kidney Disease (ALADIN) trial investigated the effect of octreotide long-acting release (LAR) versus placebo in 79 people with ADPKD with change in TKV as primary endpoint. Octreotide LAR significantly reduced TKV growth after 1 year, but not at 3 years. The effects on kidney function are more complex to interpret. The decline in measured GFR (mGFR) from baseline to year 3 was not significantly different in the octreotide LAR group compared to placebo, but it was significant when measured from year 1 to year 3. Unfortunately, despite careful randomization, participants in the placebo group appeared to have more severe disease, making it complicated to draw conclusions. The ALADIN 2 trial investigated the use of octreotide LAR versus placebo in 100 people with ADPKD and later-stage kidney disease (eGFR 15–40 ml/min per 1.73 m²), with TKV growth and mGFR decline as primary endpoints. In this study, octreotide LAR significantly reduced TKV growth at 1 and 3 years, but there was no significant effect on mGFR decline (neither when measured as slope from baseline to year 3, nor as slope from year 1 to 3). Despite the lack of effect on mGFR decline, people treated with octreotide LAR progressed less frequently to a composite endpoint of doubling of SCr or kidney failure compared to placebo (17.6% vs. 42.9%, respectively). This composite endpoint was, however, not a priori defined (NCT00309283). Later, a much larger study (Developing Interventions to Halt Progression of ADPKD [DIPAK-1]) that randomized 309 people with ADPKD to the somatostatin analog lanreotide or standard treatment found no
significant effect of lanreotide on the primary outcome rate of eGFR decline compared to placebo (-3.53 ml/min per 1.73 m² per year vs. -3.46 ml/min per 1.73 m², respectively), nor on the incidence of the combined endpoint worsening of kidney function (defined as a 30% eGFR decrease or start of dialysis). However, similar to earlier trials, this study also demonstrated that the rate of TKV growth was significantly reduced by a somatostatin analog. The difference between the lanreotide and control groups in the hTKV growth rate at week 120 (end-of-treatment) was -2.14% per year (95% CI: -3.14% – 1.12%; P < .001) with a rate of TKV growth of 3.55% versus 5.81% per year in lanreotide versus control subjects, respectively, corresponding with a 37% reduction in TKV growth rate with lanreotide. In this trial an even stronger effect was found on the growth rate of polycystic livers. Of note, the effect of the somatostatin analog on volume growth of the polycystic liver and kidneys is biphasic: a strong short-term decrease, and a long-term, chronic treatment effect. After 2.5 years of treatment, when the somatostatin analog was stopped, a large part of the chronic effect remained. Lastly, the Lanreotide In Polycystic kidney disease (LIPS) study also investigated lanreotide using kidney function as primary outcome in 159 people with ADPKD. It was completed in 2019, but publication of the results is still awaited (NCT02127437). Besides these 4 studies with a relatively long treatment duration, several other more short-term studies have been performed, for instance by Hogan et al. and Van Keimpema et al. In general, the results of these studies align with the aforementioned studies.

In general, somatostatin analogues are well-tolerated but some side effects of somatostatin analogues may be more prominent in people with ADPKD. Besides their general side effects, such as causing gastrointestinal discomfort, hyperglycemia (especially with pan-somatostatin receptor analog pasireotide), and bradycardia, there may be ADPKD-specific side effects. In the aforementioned larger scale RCT, a higher incidence of hepatic cyst infections (mainly in people with a previous history of cyst infection) was identified in a single study, and gallstone formation has been noted with lanreotide compared to control treatment, with associated biliary complications such as cholecystitis and pancreatitis. Chapter 5 discusses this issue in more detail.

Certainty of evidence

The overall certainty of evidence was graded as moderate based on the certainty of evidence for the critical outcomes of CKD progression, TKV progression, and serious adverse events, supported by low certainty of evidence for other outcomes (Supplementary Table S16). The 5 RCTs mostly had some limitations related to lack of blinding or a high rate of missing data and possible selective reporting. In addition to the moderate certainty of evidence for the critical outcomes noted above, there was low certainty of evidence for the critical outcomes, other adverse events (liver cyst infections, gallstones, other gastrointestinal), and QoL due to sparseness of evidence (one study per outcome). There was very low certainty of evidence for the critical outcome of pain due to sparseness and imprecision. Based primarily on the moderate certainty of evidence for CKD and TKV progression and moderate and low certainty of evidence for various adverse events, we concluded that the overall certainty of evidence is moderate (Level B).
Values and preferences

Although somatostatin analogues do not have clear kidney-protective effects, there may be a role for these agents in reducing volume-related complaints in ADPKD, especially in people with a high combined polycystic kidney and liver volume.\textsuperscript{383} The beneficial effect of these drugs for this indication should be weighed against the side effects of these drugs, such as the general side effects as impairing glucose metabolism and lowering heart rate, and side effects that may be more prominent in people with ADPKD, such as gallstone formation and pancreatitis.\textsuperscript{382}

Resource use and costs

The costs of somatostatin analogues may differ across countries and between the various agents, but in general these costs are high relative to benefits on preventing kidney failure. This limits the potential use of these agents.

Considerations for implementation

Because somatostatin analogues have not been shown to have a clear kidney-protective effect and are associated with significant side effects and high costs, their use should only be considered in people with severe complaints due to their massively enlarged polycystic organs. In addition, it seems prudent to try to assess the effect of prescribing the somatostatin analog on symptom burden (via serial questionnaires) and/or volume of the polycystic kidneys and liver (via serial imaging). In case no beneficial effects are observed, medication should be withdrawn.

Rationale

Overall, analysis of the 5 RCTs of somatostatin analogues showed that there was no benefit in slowing the progression of kidney function in people with ADPKD. Somatostatin analogues reduced TKV, especially during the first year of treatment. A large part of the effect on TKV was maintained 3 months after stopping the drug. Adverse effects of somatostatin analogues include hepatic cyst infection, biliary complications, gastrointestinal discomfort, hyperglycemia, and bradycardia. Therefore, the Work Group suggested that treatment with somatostatin analogues should only be considered in selected people with severe symptoms secondary to massive kidney enlargement where the benefit of treatment may outweigh the potential harms.

Practice Point 5.2.3.4: Somatostatin analogues should not be prescribed for the sole purpose of improving the rate of eGFR loss in people with ADPKD.

Somatostatin analogues should be prescribed to suppress the growth of polycystic livers and not to improve the rate of eGFR loss in people with ADPKD.

Research recommendations

- There may be differences in kidney-protective efficacy between the various somatostatin analogues, with octreotide potentially having more effect. For this reason, an adequately powered long-term RCT could be considered that compares octreotide to placebo in people with ADPKD and rapidly progressive disease. The primary endpoints of this trial should be a priori defined and include the rate of eGFR change during treatment, as well
as the effect on QoL in people with severe complaints related to their massively enlarged polycystic organs.

4.7. SGLT2 inhibitors
Practice Point 4.7.1: SGLT2 inhibitors should not be used to slow the rate of eGFR decline in people with ADPKD, until further research determines their efficacy and safety.

The SGLT2 inhibitors (SGLT2i) block the sodium-glucose cotransporter SGLT2 in the proximal tubule, causing a loss of glucose and sodium that stimulates the juxtaglomerular apparatus, causing a vasoconstriction in the afferent arteriole and a decrease in the intraglomerular pressure and hyperfiltration. This effect is paralleled by metabolic benefits through glucosuria. Conversely, the osmotic diuresis caused by SGLT2i may stimulate vasopressin, which has been involved in cystogenesis and progression of ADPKD.

Recent studies have demonstrated that SGLT2i have a nephroprotective and cardioprotective effect in people both with and without diabetes. The potential benefits of SGLT2i have not been specifically explored in ADPKD, because the major trials of SGLT2i in nondiabetic CKD excluded people with ADPKD. SGLT2i have been investigated in rat (PCK and Han:SPRD) and mouse (Pkd1) models of polycystic kidney disease, with inconsistent results. Studies are needed to confirm the safety and potential efficacy of SGLT2 inhibitors in people with ADPKD. Research is also needed to understand the metabolic effects of SGLT2i in this population.

4.8. Complementary medicines
Practice Point 4.8.1: Complementary medicines or supplements should not replace standard medical treatments and people with ADPKD should share their intended or ongoing use of complementary medicines with their healthcare team.

Complementary medicines or supplements are defined as a broad group of therapies that are available without prescription. Examples include herbal medicines, nutritional supplements, vitamins and minerals, homeopathic preparations, aromatherapy, and traditional Chinese and Ayurvedic medicines. Typically, the use of these medicines is initiated by people based on information obtained from a broad range of sources. Presently, there is no evidence to support that specific types of complementary medicines slow kidney disease progression in people with ADPKD and there is little or no information about potential harms. However, this is because there has been very little research undertaken in this field.

To date, only 3 clinical trials have been conducted that involved niacinamide, curcumin, and ketone supplements. In general, the studies have been small and underpowered, and overall had no beneficial effects on ADPKD progression were demonstrated. Although most complementary medicines in high-income countries have been assessed by regulatory authorities and may be considered as having a low risk of harm at recommended dosages for people who are generally healthy, many others are available via online purchasing, therefore quality and safety is
uncertain, and their potential harms in people with CKD in general and ADPKD specifically is unknown. Due to the uncertainty and paucity of evidence, people with ADPKD should discuss their usage of complementary medicines with their healthcare team.
CHAPTER 5. POLYCYSTIC LIVER DISEASE

5.1. Diagnosis and staging of PLD

Polycystic liver disease (PLD) is a hereditary disease characterized by the presence of multiple (arbitrarily defined as >10 in clinical practice) fluid-filled cysts scattered throughout the liver.\(^{384}\) The phenotype may be restricted to the liver in isolation in ADPKD but PLD may also occur in conjunction with kidney cysts in hereditary polycystic kidney disease. For research purposes, the following phenotypical characteristics have been used to assign the diagnosis of PLD within ADPKD families: a) the presence of any liver cyst when it occurs in association to ADPKD,\(^{385}\) b) the presence of 1 cyst before 40 years of age or 4 cysts after 40 years of age in families with PLD with no or only a few kidney cysts (ADPLD),\(^{386}\) or c) arbitrarily in the presence of >10 liver cysts (or >20 liver cysts in other publications) in absence of an family history of ADPKD or ADPLD.\(^{384,387}\) This chapter addresses ADPKD-related PLD. While the majority of people with ADPKD possess liver cysts and prevalence of liver cysts increases with age, most people will not develop clinically symptomatic PLD.\(^{388}\) The presence of liver cysts, even in advanced PLD, will usually not impact the synthetic or secretory capacity of the liver. However, symptoms can ensue related to the mass effects of a large cystic liver exerting pressure on diaphragm and abdominal wall, compressing other abdominal organs and vascular structures.

Practice Point 5.1.1: The liver should be included when abdominal imaging is performed, preferably using CT scan or MRI, in people with ADPKD to characterize the severity of PLD.

Multiple classifications for PLD have been proposed based on liver volume and cyst characteristics (Table 9).\(^{389-392}\) The first proposed staging systems aimed to identify people eligible for cyst volume surgery or liver transplantation based on cyst number, size, and distribution.\(^{390,391}\) Afterwards, staging systems were proposed that aimed to differentiate across disease severity based on cyst number and liver volume.\(^{388,389,392}\) Liver volume correlates with presence and severity of symptoms in PLD.\(^{393}\) Therefore, liver volume should be evaluated whenever abdominal imaging is performed to assess disease severity in ADPKD. Two studies used height-adjusted total liver volume (htLV) for this purpose but used different thresholds: PLD was classified as mild, moderate, or severe with htLV thresholds of <1600 ml/m, 1600-3200 ml/m and >3200 ml/m in one study, while the other (HALT-PKD study) used different htLVs (mild <1000 ml/m, moderate 1000–1800 ml/m, and severe >1800 ml/m).\(^{385,389}\) A major limitation of all previously described classification systems is that they do not factor in the age of the person. Recently, the HALT and CRISP PKD investigators have proposed a classification based on height-adjusted liver cyst volume (htLCV) adjusted for age.\(^{394}\) HtLCV growth was calculated from a nonzero theoretical starting point and people were grouped according to their annual htLCV growth: class A: <5%; B: 5%–10%; C:10%–15%; D: 15%–20%; and E: >20%. People with substantial liver cyst burden (Class C, D or E) could be considered to have severe PLD. The main limitation of this classification is that it has not yet been validated in independent populations.
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<th>Staging system</th>
<th>Classes</th>
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| Gigot et al. 1996 | • Type I: a limited number (<10) of large cysts (>10 cm)  
• Type II: diffuse involvement of liver parenchyma by multiple medium-sized cysts with remaining large areas of noncystic liver parenchyma  
• Type III: massive, diffuse involvement of liver parenchyma by small- and medium-sized liver cysts and only a few areas of normal liver parenchyma between cysts | Patient selection for cyst fenestration | • Did not factor in age/liver growth  
• No information regarding prognosis |
| Schnelldorfer et al. 2009 | **Type A:**  
• Symptoms: absent or mild  
• Cyst characteristics: any  
• Areas of relative normal liver parenchyma: any  
• Isosectoral portal vein or hepatic vein occlusion of preserved sector: any  
**Type B:**  
• Symptoms: moderate or severe  
• Cyst characteristics: limited no large cysts  
• Areas of relative normal liver parenchyma: ≥2 sectors  
• Isosectoral portal vein or hepatic vein occlusion of preserved sector: absent  
**Type C:**  
• Symptoms: severe (or moderate)  
• Cyst characteristics: any  
• Areas of relative normal liver parenchyma: ≥1 sector  
• Isosectoral portal vein or hepatic vein occlusion of preserved sector: absent  
**Type D:**  
• Symptoms: severe (or moderate)  
• Cyst characteristics: any | Patient selection for volume reducing therapy and liver transplantation | • Did not factor in age/liver growth  
• No information regarding prognosis |
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| Qian et al. 2003<sup>392</sup> | • Grade 0: 0 cysts  
• Grade 1: 1–10 cysts  
• Grade 2: 11–20 cysts  
• Grade 3: >20 cysts  
• Grade 4: >20 cysts and symptomatic hepatomegaly | Determination of disease severity | • Did not factor in age/liver growth  
• No information regarding prognosis |
| Kim et al. 2015<sup>389</sup> | • Mild: htTLV <1600 ml/m  
• Moderate: 1,600 ≤ htTLV <3200 ml/m  
• Severe: htTLV ≥3200 ml/m | Determination of disease severity | • Did not factor in age/liver growth  
• No information regarding prognosis |
| Hogan et al. 2015 (HALT-PKD)<sup>385</sup> | • Mild: htLV <1000 ml/m  
• Moderate: htLV between 1000 and 1800 ml/m  
• Severe: htLV >1800 ml/m | Determination of disease severity | • Did not factor in age/liver growth  
• No information regarding prognosis |
| Bae et al. 2022 (HALT-PKD and CRISP)<sup>394</sup> | • Class A: htLCV growth <5%  
• Class B: htLCV growth 5%–10%  
• Class C: htLCV growth 10%–15%  
• Class D: htLCV growth 15%–20%  
• Class E: htLCV growth >20% | Determination of disease severity | • Not validated in independent populations |
| Sierks et al. 2022<sup>395</sup> | Normalized age-adjusted liver volume  
• Progression Group I: <3.3% growth rate/year  
• Progression Group II: 3.3–6.6% growth rate/year  
• Progression Group III: >6.6% growth rate/year | Individual prognostication | • Not validated in independent populations  
• Normalized against a standard baseline liver volume of 850 ml/m at the age of 20 years (fold over |
<table>
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<td>standard baseline TLV at age 20 = nTLV)</td>
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*Table 9. Classifications for polycystic liver disease (PLD).* CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; HALT-PKD, HALT Progression of Polycystic Kidney Disease; hLCV, height-adjusted liver cyst volume; hLV, height-adjusted total liver volume.
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.

People should be advised that liver cysts in ADPKD typically develop later than kidney cysts. They are eventually seen in 90% of people with ADPKD, are more numerous and larger in women than in men, and typically remain asymptomatic throughout life. People with ADPKD should be advised that liver failure (the development of severe acute liver injury with impaired synthetic function and altered mental status) or the need for liver transplant is extremely unlikely to occur. However, if a person experiences symptoms due to hepatomegaly that affect QoL, such as abdominal pain, early satiety, reflux, shortness of breath, dyspnea, weight loss, or loss of appetite, they should report these to their physician.

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.

People with ADPKD may experience a range of abdominal complaints. Typically, increased kidney or liver cyst burden will cause symptoms when adjacent structures including abdominal wall, diaphragm, stomach, bile or pancreatic ducts, or intestine are impacted. Symptoms commonly observed in people due to significant PLD burden include diffuse or localized abdominal pain, back pain, early satiety, and shortness of breath. The source of these symptoms should be investigated to differentiate between PLD-related symptoms and symptoms that originate for causes unrelated to PLD (e.g., irritable bowel syndrome, kidney, or gallstones, diverticular disease of the colon).

Abdominal wall and diaphragmatic hernias, and gastroesophageal reflux are often present, while other complications in PLD are rarely observed. Rare complications may cause symptoms when cysts compress the inferior vena cava (lower limbs edema), hepatic veins (ascites, venous outflow obstruction), or portal vein (portal hypertension).

Abdominal imaging plays a pivotal role in determining the source of abdominal symptoms. Ultrasound, CT, or MRI may aid in the differentiation and identification of the origin of pain (e.g., kidney, liver, or other adjacent structures). While CT and MRI provide more precise imaging, ultrasound can be useful as an initial imaging tool to sort out potential causes for the symptoms.

Typically, liver function remains unaffected in people with PLD even in the most severe cases. Occasional elevations in alkaline phosphatase and gamma-glutamyl transferase may be observed but have no clinical consequence. In addition, compression of intrahepatic bile ducts by hepatic cysts may lead to (mild) intrahepatic biliary dilatation in the absence of clinically relevant cholestasis. Biochemical follow-up of asymptomatic people is not warranted in view of the intact functional capacity of the remaining liver tissue. Consequently, liver biomarkers (e.g., bilirubin, alkaline phosphatase, gamma-glutamyl transferase, ALT, and AST)
should not be tested periodically in people with ADPKD and PLD unless they are taking tolvaptan (see Chapter 4).

**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).**

Typically, people with PLD are asymptomatic, especially those who have a limited number of liver cysts without appreciably increased TLV. Symptoms of PLD arise when liver cysts increase in size and exert pressure against adjacent structures. The type of symptoms depends on the structure that is affected and can be grouped as (Figure 30):

- Overall liver size
- Pressure against diaphragm and lungs
- Pressure against the stomach
- Cyst complications
- Intracystic
- Extracystic

**Figure 30. Symptoms of polycystic liver disease (PLD).** Normal cysts labeled yellow, recurrent cyst infection labeled grey, recurrent cyst hemorrhage labeled red, cyst obstructing the bile ducts labeled green, cysts obstructing hepatic veins labeled blue.

Symptom burden is highly relevant when considering treatment for PLD. People with symptomatic PLD suffer from a decrease in QoL, specifically with respect to mental health measures of QoL. However, general QoL questionnaires lack disease specificity to adequately capture PLD-related symptom burden. Two disease-specific symptom questionnaires, the PLD-Q and POLCA, have been developed and validated. The PLD-Q accurately and reliably assesses PLD symptom severity and is used to evaluate treatment efficacy for PLD-related treatments. In contrast, the POLCA was specifically designed to triage people with PLD for liver transplantation. The POLCA aids physicians in differentiating between people who will benefit from liver transplantation and people who will not.
Research recommendations

- Research is needed to develop a validated staging system for PLD that incorporates age, biological gender, liver volume/liver cyst volume, cyst number and distribution, and presence of dominant cysts in relation to patient symptoms and complications.
- A definition of severe PLD that identifies people who would benefit most from therapy is needed.
- Research is needed to develop and validate practical and accurate imaging tools to measure total liver volume (TLV) and liver cyst volume (LCV) in people with PLD.

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 counselled about the benefits and potential harms of sex hormone therapy.

Women with ADPKD are more often affected with PLD (>80%) compared to men. This occurs in both ADPKD and isolated ADPLD. PLD in women with ADPKD occurs earlier (~9 years) and is associated with a higher risk of aggressive cyst growth as compared to men. Approximately 85% of people with ADPKD and symptomatic PLD presenting for medical care are women. TLV is greater in women compared to men, and >80% of liver transplantations performed for symptomatic PLD occur in women.

There is an age-dependent growth pattern of PLD in people with ADPKD. In women <48 years of age, median liver growth is 2.65% per year compared to 0.09% per year in those ≥48 years of age. This demarcation in age appears to coincide with menopause and may support the concept that there is an aggressive, premenopausal TLV growth pattern that lessens postmenopausally.

Observational studies have demonstrated that yearly exposure to low-dose estrogen-containing oral contraceptives is associated with a 1.45% greater TLV in women with ADPKD (15.5% greater TLV for each decade of use). A case-control study of 19 post-menopausal women with ADPKD and PLD demonstrated that estrogen-replacement therapy associated with a 7% annual increase in TLV, while those not receiving estrogen-replacement therapy demonstrated a 2% annual decline in TLV. One study suggested a relationship between number of pregnancies and PLD severity, but this observation has not been validated. The role of pregnancy in ADPKD and its relation to PLD is discussed further in Chapter 8, as are alternative contraceptive options to estrogen-containing contraceptive medications.

Research recommendations

- Studies are needed to define the natural history of PLD in ADPKD.
- Studies are needed to determine the effects of pregnancy on TLV growth.
- Studies are needed to determine the effects of phytoestrogens on TLV growth.
- Studies are needed to determine the effects of different estrogen exposures (e.g., estrogen-based conception, in vitro fertilization [IVF], hormone substitution therapy, estrogen or progesterone based intrauterine devices [IUD]) on TLV growth.
- Studies are needed to compare the relative impact of progestins versus estrogen on TLV growth.
- Studies are needed to identify risk factors for the development of liver cysts in young people with ADPKD.
- Studies are needed to identify the young people with ADPKD who are at risk for greater increases in TLV.

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.

People with ADPKD should be advised of the potential harms of following so-called “dietary advice” to treat PLD as suggested by people on online forums or advertised on unreliable websites. People with PLD should instead adhere to diet and lifestyle advice for people with ADPKD and various severities of CKD (Chapter 7).

Practice Point 5.2.2.2: People with symptomatic PLD should be assessed for sarcopenia and malnutrition.

Malnutrition is an important complication of PLD. Malnutrition results primarily from the mass effect of TLV that reduces the stomach capacity resulting in reduced caloric intake. Clinical manifestations of this phenomenon include early satiety, nausea, and vomiting, particularly after ingestion of large portions of food. These mass-related symptoms are captured reliably using the PLD-Q. Symptoms result in an inadequate intake of nutrients, weight loss, and sarcopenia which is frequently seen in people with severe hepatomegaly. The added weight of enlarged polycystic livers can mask sarcopenia in these people who are losing lean body mass but whose overall weights are not reduced as significantly.

For this reason, the use of objective sarcopenia criteria is warranted. Sarcopenia and malnutrition can be assessed through various methods (Table 10). Measurement of skeletal muscle index in a single CT slice at the third lumbar vertebra is the most accurate method to diagnose sarcopenia. Nutritional status and malnutrition can be assessed with bioelectrical impedance analysis, grip strength, mid-arm circumference, and detailed nutritional assessments by nutritionists. Weight loss and 24-hour calorie counts can also be used as general markers of nutritional status.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Definition sarcopenia or malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle index</td>
<td>Skeletal muscle mass measured at 3rd lumbar vertebrae. Sarcopenia defined as SMI &lt;38.5 cm²/h² in females and &lt;52.4 cm²/h² in men</td>
</tr>
<tr>
<td>Technique</td>
<td>Definition sarcopenia or malnutrition</td>
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<tr>
<td>-----------------------------------</td>
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<tr>
<td>Bioelectrical impedance analysis</td>
<td>Sarcopenia:</td>
</tr>
<tr>
<td></td>
<td>- &lt;5.7 kg/m² in females</td>
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<tr>
<td></td>
<td>- &lt;7.0 kg/m² in males</td>
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<tr>
<td>Grip strength</td>
<td>Sarcopenia:</td>
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<tr>
<td></td>
<td>- female &lt;18 kg</td>
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<tr>
<td></td>
<td>- male &lt;26 kg</td>
</tr>
<tr>
<td>Mid-arm circumference</td>
<td>Severe malnutrition:</td>
</tr>
<tr>
<td></td>
<td>- females: &lt;23.1 cm</td>
</tr>
<tr>
<td></td>
<td>- males: &lt;23.8 cm</td>
</tr>
<tr>
<td>Detailed nutritional assessment</td>
<td>Includes: clinical examination (history and physical examination), anthropometric measurements, diagnostic tests (laboratory tests and body composition studies) and dietary assessment.</td>
</tr>
</tbody>
</table>

Table 10. Methods to assess sarcopenia and malnutrition. SMI, skeletal muscle index.

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

Malnutrition and sarcopenia are frequently observed in people with PLD and severe hepatomegaly. Sarcopenia serves as an important criterion for liver transplantation in PLD in the setting of normal liver function which complicates proper use of traditional Model for End-stage Liver Disease (MELD)-based liver allocation. However, a person’s nutritional status including sarcopenia negatively impacts survival after liver transplantation and prehabilitation in preparation for liver transplant is advised.

People with sarcopenia and PLD often consume small portions of food spread throughout the day. No data are available that examine the effects of diet and exercise interventions on sarcopenia status. However, current literature consistently shows that sarcopenia negatively impacts outcomes after liver transplantation. Dieticians and physical therapists should guide people with PLD and sarcopenia to optimize their nutrition status and physical condition.

**Research recommendations**
- Research is needed to develop and validate practical and accurate imaging tools to measure sarcopenia in people with PLD.
- Implementation tools for the measurement of sarcopenia are needed.
- Studies are needed to determine the efficacy of alternative tools to diagnose sarcopenia in people with PLD.
- Studies are needed to determine the nature and impact of intensive nutritional and physiotherapeutic interventions on treatment outcomes in people with PLD and malnutrition or sarcopenia.

**5.2.3. Management**
**Practice Point 5.3.3.1:** Treatment for PLD should be performed in centers of expertise.
Sufficient expertise is required to minimize the risk of complications from surgery for PLD and manage side effects of therapy. Surgery for PLD may be complicated in view of the variety of anatomical deformations that are present and the limited intra-abdominal space, particularly in people with large polycystic kidneys. Cases should be discussed within multidisciplinary teams to evaluate the benefits and harms of each treatment option. Treatment for PLD should also be performed in centers of expertise to prevent exposing patients to complications and side effects of ineffective PLD treatment options.

**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.

Since symptoms in PLD often correlate with the extent of cystic enlargement and hepatomegaly, treatments usually seek to reduce cyst volume and hepatomegaly. This goal can be achieved through pharmacological, interventional radiology, and surgical means, depending on cyst characteristics and availability of experience at the medical center.\(^ {384, 418} \)

Medical therapies, as discussed in subsequent recommendations and practice points, are typically appropriate for people with marked hepatomegaly caused by a multitude of small- and medium-sized liver cysts distributed throughout all liver segments.

Interventional radiological therapies include aspiration sclerotherapy and transarterial embolization of hepatic arteries (Table 11). The expertise of the interventional radiologist performing these procedures is critical for their safety and success.

*Aspiration sclerotherapy* is performed in people with one or few large dominant cysts accounting for symptomatic hepatomegaly or for symptomatic compression of bile ducts, abdominal organs, inferior vena cava, hepatic veins or portal vein.\(^ {419, 420} \) Different sclerosing agents have been used as sclerosant without evidence for superiority of any of these agents.\(^ {419} \) The final result is achieved approximately 3–6 months after the procedure, and we advise against reintervention in the first months post procedure. Usually, cysts measuring ≥5 cm in diameter are amenable for successful sclerotherapy. Large cysts may require additional measures such as increasing the dose of sclerosant, increasing instillation time or a repeat sclerotherapy treatment. The procedure is considered safe with limited side effects (mostly postprocedural pain) without reported mortality.

The evidence for *transarterial embolization* of liver cysts is limited to case series. This procedure is performed in few centers in Japan, Korea, and France. It requires hospitalization for 3–5 days for pain control and prevention and treatment of postembolization syndrome. It results in a mean reduction in liver volume of 13% at 3 and 28% at 51 months, with a reported symptomatic improvement in approximately 70% of the people.\(^ {421, 422} \)
Surgical interventions include laparoscopic cyst fenestration, combined partial hepatectomy and cyst fenestration, and liver transplantation. As with interventional radiology procedures, the expertise of the surgeon, surgical team, and supportive multidisciplinary services is critical for the safety and success of these procedures.

**Laparoscopic cyst fenestration** is a surgical technique that is used to treat large liver cysts located anteriorly and caudally. Wide deroofing of the cysts is important to prevent recurrence of the cysts. Multiple large cysts can be targeted with this technique. Symptomatic recurrence occurs in one-third of the patients. His surgical approach comes with higher morbidity and mortality compared to aspiration sclerotherapy. 405

**Combined partial hepatectomy and cyst fenestration (PHCF)** of the remnant liver is feasible in people with massive, highly symptomatic PLD when at least one hepatic sector is relatively spared and the afferent and efferent sectoral vasculature is patent to assure adequate liver reserve. 391, 423 This surgery is technically challenging and should only be performed in centers of expertise. It is associated with a greater complication rate, longer operative time, and greater blood loss compared to partial hepatectomy in people with noncystic livers. Transient ascites with prolonged drainage and biliary leaks are among the most common postoperative complications. A prospective study of 16 people using the PLD-Q showed that symptoms significantly decreased after surgery with the most impact seen on early satiety and dyspnea. 424 QoL also improved. In the largest series of people (n=186) published to date, PHCF led to a significant decrease in liver volume (-61%), major perioperative complications (Clavien III/IV, i.e. requiring surgical, endoscopic or radiological intervention or ICU management) occurred in 21% of the people and operative mortality (<90 days) in 2.7%. 425 Eleven people eventually had liver failure develop, received liver transplants, or had liver-related deaths. Because previous liver surgery and development of adhesions increase the difficulty of liver transplantation, PHCF should be considered in patients where long-term satisfactory results are anticipated and not in those who will likely require liver transplantation.

**Liver transplantation** is the only curative intervention for PLD and is discussed below.
<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Liver phenotype</th>
<th>Efficacy</th>
<th>Morbidity and mortality</th>
</tr>
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<tbody>
<tr>
<td>Aspiration sclerotherapy (systematic review of 16 studies, 526 people with hepatic cysts)(^{419, 420})</td>
<td>One or few large dominant cysts accounting for symptomatic hepatomegaly or for symptomatic compression of bile ducts, abdominal organs, inferior vena cava, hepatic veins or porta</td>
<td>• Symptomatic improvement: 72%–100% &lt;br&gt; • Individual cyst volume reduction: 76%–100% (^{419, 420})</td>
<td>• Minor complications: 5%–90% &lt;br&gt; • Mortality: &lt;1.0% (not reported) (^{419, 420})</td>
</tr>
<tr>
<td>Transarterial embolization (2 retrospective studies, 40 people with PLD)(^{421, 422})</td>
<td>Diffuse symptomatic liver cysts with at least one segment of functioning liver remaining intact and no indication for alternative treatment options.</td>
<td>• Symptomatic improvement: 72%–93% &lt;br&gt; • Need for reintervention: 15% &lt;br&gt; • Mean reduction in TLV: 13% at 3 months, 28% at 51 months (^{421, 422})</td>
<td>• Post-embolization syndrome 100% &lt;br&gt; • Complications 7.5% &lt;br&gt; • No major complications (^{421, 422})</td>
</tr>
<tr>
<td>Laparoscopic cyst fenestration (metanalysis of 15 studies, 146 people with PLD)(^{405})</td>
<td>Large liver cysts located anteriorly and caudally</td>
<td>• Symptomatic recurrence: 33.7% &lt;br&gt; • Need for reintervention: 26.4% (^{405})</td>
<td>• Complications: 29.3% &lt;br&gt; • Clavien III-IV perioperative complications: 7.2% &lt;br&gt; • Mortality: 2.3% (^{405})</td>
</tr>
<tr>
<td>Combined partial hepatectomy and cyst fenestration (retrospective, single center, 186 people with PLD)(^{391, 423, 424})</td>
<td>Massive, highly symptomatic PLD when at least one hepatic sector is relatively spared and the afferent and efferent sectoral vasculature is patent to assure adequate liver reserve</td>
<td>• Median reduction in TLV: 61% postoperative and at 8 years &lt;br&gt; • Symptomatic improvement: 94% (^{391, 423, 424})</td>
<td>• Clavien III-IV perioperative complications: 21% &lt;br&gt; • Mortality: 2.7% &lt;br&gt; • Survival: 96%, 93%, 86%, and 78% at 1, 5, 10, and 15 years, respectively (^{391, 423, 424})</td>
</tr>
<tr>
<td>Liver transplantation (retrospective reviews of 271 and 58 people with PLD)(^{426, 427})</td>
<td>Massive PLD and 1) high symptom burden or, 2) sarcopenia or, 3) PLD related complications, and a contraindication or failure of alternative treatment options(^{376})</td>
<td>Only curative treatment option</td>
<td>• Postoperative complications: 46% &lt;br&gt; • Mortality: 9% &lt;br&gt; • 1-year patient survival: 85%–95% &lt;br&gt; • 5-year patient survival 77%–92% (^{376})</td>
</tr>
<tr>
<td>Treatment option</td>
<td>Liver phenotype</td>
<td>Efficacy</td>
<td>Morbidity and mortality</td>
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</tr>
<tr>
<td>Somatostatin analogues&lt;sup&gt;378, 380, 428, 429&lt;/sup&gt;</td>
<td>People with volume related symptoms</td>
<td>• Reduction in annual liver growth rate of 5.9%–14.9% after 1–3 years of follow-up</td>
<td>• Treatment was well-tolerated. Dose adjustments were made in case of side-effects (e.g., gastrointestinal complaints or hyperglycemia). • Pasireotide has the highest hyperglycemia risk</td>
</tr>
</tbody>
</table>

*Table 11. Treatment options in polycystic liver disease (PLD).*
Recommendation 5.2.3.1: We suggest prescribing long-acting somatostatin analogues in people with ADPKD and markedly enlarged polycystic liver with severe volume related symptoms (2B).

Practice Point 5.2.3.3: When long-acting somatostatin analogues are prescribed, the effect on symptom burden and/or volume of polycystic liver and kidneys should be evaluated after 6 months. When beneficial effects of therapy are not observed, somatostatin analogues should be discontinued.

This recommendation places a high value on the reduction in TLV and TKV, and the prevention of liver transplantation in people with ADPKD and PLD. The recommendation places a low value on the uncertainty regarding QoL and the potential costs associated with this therapy.

Key information

Balance of benefits and harms

Long-acting somatostatin analogues (e.g., lanreotide, octreotide, and pasireotide) reduce 3′,5′-cAMP levels in cystic cholangiocytes and inhibit cholangiocyte and kidney epithelial cell proliferation and fluid secretion. Four RCTs assessed the effect of somatostatin analogues on PLD with a follow-up of ≥1 year. These trials provide moderate evidence that somatostatin analogues reduce TLV in people with ADPKD and ADPLD compared to placebo. Somatostatin analogues also reduce the rate of growth of polycystic kidneys but did not slow the rate of eGFR decline. Adverse events include mild gastrointestinal symptoms (e.g., steatorrhea, and transient abdominal cramps), cholelithiasis, hypo- and hyperglycemia, and alopecia. Hyperglycemia and diabetes are more common with pasireotide compared to lanreotide and octreotide. An individual patient meta-analysis demonstrated that young women benefit the most from somatostatin analogues.

Certainty of evidence

The overall certainty of evidence was graded as moderate (Supplementary Table S17). Four RCTs, with mostly moderate risk of bias related to either lack of blinding or possible selective outcome reporting, provided evidence. They all reported on the effect of somatostatin analogues on the critical outcome liver size, providing moderate certainty of evidence. One small study provided sparse, thus very low certainty evidence, for the critical outcomes pain and QoL, and several important harms. The trials did not evaluate other critical outcomes. Therefore, overall, there was moderate certainty evidence (Level B), which, as noted, pertained primarily to liver size.

Values and preferences

The Work Group judged that many people with massive polycystic livers would choose treatment with somatostatin analogues due to the efficacy benefits for TLV and reversible side effects of the therapy. A special emphasis was also placed on preventing liver transplantation. Consequently, the Work Group deems somatostatin analog therapy to be a beneficial treatment.
modality in people with symptomatic PLD. The expected beneficial effects and side effects of this therapy should be discussed with the person before treatment is initiated.

Resource use and costs

Somatostatin analogues are an expensive medical therapy that is not covered by insurance in every country. Physicians should discuss the potential costs with their patients before initiating somatostatin therapy.

Considerations for implementation

It is unknown whether the effect of different specific somatostatin analogues differ, particularly between octreotide long-acting release (LAR) and lanreotide. Pasireotide does not appear to be more effective, while adverse effects (e.g., hyperglycemia and diabetes) are more common.

The effect of somatostatin analogues on volume of polycystic liver and kidneys, as well as symptom burden should be evaluated after 6 months of treatment. Therapy should be discontinued when inhibition of liver growth by long-acting somatostatin analogues is no longer observed. Somatostatin analogues should be prescribed to suppress the growth of polycystic livers and not to improve the rate of eGFR loss in people with ADPKD.

Rationale

The available RCTs provide moderate evidence that somatostatin analogues reduce total liver and kidney volume in PLD. Somatostatin analogues should be used in symptomatic people with large polycystic livers in view of the potential side effects and associated costs.

Practice Point 5.2.3.4: Ursodeoxycholic acid, mTOR inhibitors, and vasopressin-2 (V2) receptor antagonists should not be used to slow liver growth in people with PLD.

Medical alternatives to somatostatin analogues have been investigated. Preclinical studies demonstrated that ursodeoxycholic acid targets cAMP in cystic cholangiocytes and reduces cholangiocyte proliferation. A clinical trial found that ursodeoxycholic acid does not reduce TLV in people with PLD.

Mammalian targets of rapamycin (mTOR) inhibitors used after kidney transplantation appeared to decrease TLV in a cohort study, but this was not observed in a short-term RCT that compared octreotide monotherapy with octreotide plus everolimus treatment in nontransplanted people with PLD. In addition, mTOR inhibitor-related toxicity impedes its application in clinical practice for PLD.

V2 receptor antagonists directly affect intracellular cAMP levels in the kidney tubular cells expressing the V2 receptor and are a potential treatment for PLD. It was long thought that V2 receptors were absent from cystic cholangiocytes, but a recent study discovered V2 receptors in both animal and human cholangiocytes. In addition, a case report describes drastic TLV
reduction in a person who used a $V_2$ receptor antagonist.\textsuperscript{435} However, there are no interventional trials in people with PLD. Therefore, currently, these drugs should not be used solely to inhibit liver cyst growth. $V_2$ receptor antagonists are recommended to slow the rate of kidney function decline in certain people with ADPKD who are at risk for rapid disease progression (Chapter 4).\textsuperscript{436}

**Practice Point 5.2.3.5: People with PLD should be referred for liver transplantation in the event of massive PLD in the absence of contraindications or alternative treatment options.**

Liver transplantation is the only curative treatment for PLD.\textsuperscript{384} People with PLD comprise 1.5\% of the liver transplantationsthat are currently performed worldwide. Outcomes after transplantation are excellent with high patient and graft survival rates (patient survival at 1 year 85\%–95\%; at 5 years 77\%–92\%; graft survival at 1 year 94\%, at 5 years 88\%);\textsuperscript{426, 427} however, the decision-making process with respect to timing of the transplantation is complex. Liver transplantations are performed on a sickest-first principle in most allocation systems and MELD scores are commonly used for this purpose.\textsuperscript{414} However, disease severity for PLD is not reflected by the established organ allocation systems, and people with PLD are often transplanted based on exception criteria, which vary from country to country.\textsuperscript{398, 437–439}

The most important parameters that establish an indication for liver transplantation in people with PLD are: 1) the presence of massive PLD in combination with 2) low QoL, 3) sarcopenia or PLD-related complications, and 4) contraindications or failure of alternative treatment options (Figure 31). TLV can be assessed using CT or MRI scans, preferably with concomitant TKV measurements. QoL and symptom burden may be captured with QoL and symptom severity questionnaires.\textsuperscript{403, 440} Sarcopenia may be assessed with various methods of which CT-based skeletal muscle index is most reliable. Malnutrition can also be assessed through a variety of standard measurements. An important complication that may hasten liver transplantation is recurrent, refractory liver cyst infections, or hepatic vein obstruction.\textsuperscript{441} PLD-related pitfalls regarding liver transplantation are illustrated in Figure 23.
Alternative treatment options should be explored by patients and physicians before a liver transplantation is considered in view of the complexity and invasiveness of this procedure. PLD is considered one of the most technically challenging indications for liver transplantation. The massive hepatomegaly complicates manipulation of the liver for explantation and there is an increased risk of tearing fragile liver veins or caval veins which may result in massive blood loss and intraoperative death. The procedure can be further complicated by postoperative bile leakage, bile duct stenosis, hepatic artery thrombosis. Explantation may be complicated or even impossible in the presence of adhesions after previous PLD surgeries, in particular liver resection. For this reason, we advise against performing liver resection in people with PLD who are unlikely to have long-term satisfactory results from the resection and are likely to require a future liver transplantation.

Practice Point 5.2.3.6: People with PLD should be referred for combined kidney-liver transplantation when there is an indication for liver transplantation and the person has severely impaired kidney function (eGFR of <30 ml/min per 1.73 m²).

In people with ADPKD and an indication for liver transplantation with severely impaired kidney functions (eGFR of <30 ml/min per 1.73 m²), referral for combined kidney-liver
transplantation is advised. Because eGFR may overestimate kidney function in people with malnutrition, direct GFR measurements should be considered in people with borderline eGFR (30–45 ml/min per 1.73 m²). Kidney function will deteriorate as part of the natural course of ADPKD and liver transplantation will accelerate loss of kidney function. A combined liver-kidney transplantation may provide considerable postprocedural benefits over sequential organ transplantations in these people.⁴⁴²,⁴⁴³

**Research recommendations**

- Studies are needed to identify people specifically suitable for somatostatin analog therapies, cyst reduction procedures, and liver transplantation.
- Studies are needed to identify people who will benefit from preemptive PLD treatment (particularly somatostatin analogues which are more effective in younger women) prior to the development of severe PLD.
- An RCT comparing aspiration sclerotherapy and cyst fenestration to establish the relative efficacy and safety of these procedures is needed.
- Studies are needed to determine the effect of somatostatin analogues on symptom severity and presence of side effects of treatment.
- Studies are needed to investigate new medical alternatives for the treatment of symptomatic PLD.
- Studies are needed to evaluate the impact of V2 receptor antagonists on the rate of increase in TLV.
- Research is needed to establish a single organ allocation system with uniform partial and total liver transplantation criteria for PLD.

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 (Figure 33).
Figure 33. Proposed algorithm to diagnose liver cyst infections. CT, computed tomography; $^{18}$FDG PET-CT, positron emission tomography with $^{18}$F-2-deoxy-2-fluoro-glucose integrated with computed tomography; Ga67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga et al.\textsuperscript{212}

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

Liver cyst infection is an infrequent complication that is difficult to diagnose and requires immediate initiation of appropriate treatment, often empirically, with broad-spectrum antibiotics. People on dialysis and after kidney transplant are more susceptible to liver cyst infection.

The diagnosis of liver cyst infection is based on clinical parameters, blood cultures, imaging, and response to antibiotic treatment. Blood cultures should always be obtained to optimize antibiotic treatment. The role of conventional imaging (ultrasound, CT, or MRI) in this algorithm is 2-fold. First, imaging is used to exclude alternative sources of infection. Second, imaging can be used to localize infected cysts and assess their size and severity. Positron emission tomography with $^{18}$F-FDG PET-CT is a supportive item in the diagnostic algorithm and has an 89% sensitivity and 75% specificity, a positive predictive value of 84% and a negative predictive value of 82%.\textsuperscript{444} The diagnosis can be made without this imaging modality, yet it remains the imaging modality of choice to confirm the diagnosis in equivocal cases. Despite the diagnostic importance of $^{18}$F-FDG PET-CT, it is not approved to diagnose liver cyst infections in all countries and consequently insurance coverage may differ across geographical regions.
A cyst aspirate showing neutrophils or bacteria is the gold standard to diagnose liver cyst infection.\textsuperscript{445, 446} The specificity of this test is high, but the test has a high false-negative rate, resulting in a low negative predictive value. Therefore, a diagnostic algorithm was developed that provides an accurate diagnosis of liver cyst infection with high consensus among experts in the field of ADPKD and PLD (Figure 33).\textsuperscript{212}

**Practice Point 5.3.1.3: Empiric 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.**

Liver cyst infection should be distinguished from liver cyst hemorrhage. Both may present with localized liver pain and clinical, laboratory and imaging findings may be used to differentiate both entities.\textsuperscript{446} Cyst hemorrhage may be accompanied by elevations in body temperature, but rarely above 38.0°C/100.4°F. Ultrasound may show intracystic blood clots and fibrin wires in cyst hemorrhage, which are unusual in infected liver cysts. Hemodynamic instability is rare in people with cyst hemorrhage. Occasional (late) drops in hemoglobin levels have been reported.\textsuperscript{384, 447} Antibiotics provide no beneficial effect in cyst hemorrhage. People with cyst hemorrhage should be treated conservatively with adequate pain relief. In liver cyst infections, fever and elevated acute phase parameters (CRP and leukocytosis) are observed. The radiological features associated with liver cyst infections (e.g., altered cyst density, thickened/enhanced cyst walls) are not specific and should be used in combination with the diagnostic algorithm.\textsuperscript{448, 449} Application of the diagnostic algorithm (Figure 33) yields an approach to the diagnosis of liver cyst infection which helps to prevent unnecessary exposure to antibiotics.
5.3.2. Management

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

Liver cyst infection is a serious complication that may lead to sepsis and death if it is not adequately treated in a timely fashion. Thus, antibiotics should be administered as soon as possible after diagnosis (Figure 34). Liver cyst infections are most frequently caused by gram-negative bacteria from the Enterobacteriaceae family originating from the gastrointestinal system.\textsuperscript{450, 451} This bacterial family includes among others \textit{Escherichia spp.}, \textit{Klebsiella spp.}, and \textit{Salmonella spp.} \textit{Escherichia coli} was the most frequent isolate in urine, blood, and cyst cultures. Consequently, bacterial translocation from the gut is considered the most important route of infection for liver cysts and empiric treatment of liver cyst infections should primarily be targeted at gram-negative bacteria in the Enterobacteriaceae family.

\textbf{Figure 34. Management of liver cyst infections.} CRP, C-reactive protein
Practice Point 5.3.2.2: Empiric treatment of liver cyst infections should be initiated with a third-generation intravenous cephalosporin with or without a fluoroquinolone. After clinical stabilization, intravenous therapy can be switched to an oral fluoroquinolone, with adjustment according to culture results when available.

The success of antibiotic treatment in liver cyst infections is defined by several factors with a pivotal role for antibiotic penetrance into the cyst. Carbapenems and cefazolin penetrate poorly into liver cysts, while data from kidney cysts indicate higher intracystic drug levels may be achieved with trimethoprim-sulfamethoxazole. In clinical practice, the highest treatment efficacy is obtained with third-generation cephalosporins (in case of low risk of extended spectrum beta-lactamase presence) and fluoroquinolones (ciprofloxacin). Antibiotic monotherapy is not always successful and a recent literature suggests that combining antibiotics may lead to superior treatment outcomes. Antibiotic resistance patterns vary across geographical locations and need to be considered when choosing an empirical regime. In addition, resistant bacterial strains may arise after repeated antibiotic courses, including those given for cyst drainages and surgical procedures. When treating liver cyst infections, physicians should also take into consideration the side effects of antibiotics and method of administration. Currently, antibiotics are administered systemically (with intravenous or oral delivery) and there are no studies that investigated alternative administration methods (e.g., instillation or flushing of cysts with antibiotics). Physicians should also be mindful of side-effects associated with (long-term use) antibiotics (e.g., increased risk of aortic aneurysm, aortic dissection, or tendon injury with fluoroquinolones). Finally, cyst size determines the likelihood of success with antibiotic therapy where cysts >8 cm in diameter are less likely to respond to antibiotics alone without supportive cyst aspiration.

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

The duration of antibiotic treatment remains subject to debate. Sufficient penetrance of antibiotics and leukocytes into the infected cyst is required to clear the infection. Insufficient treatment results in recurrence of the infections and its symptoms. A prolonged treatment duration of ≥4 weeks is advised to ensure full eradication of the cyst infection. At the physician’s discretion, it may be appropriate to extend the course of antibiotics if deemed necessary. Dosages of antibiotic cleared in the kidney should be adjusted in people with CKD and kidney failure based on the remaining kidney function to prevent excessive accumulation of the drug and/or its active metabolite(s) or drug removal by dialysis. This requires person-specific tailoring of antibiotic regimes and monitoring of antibiotic drug levels whenever possible. Input from an infectious disease specialist and/or a pharmacist may be helpful for appropriate antibiotic selection and dosing. In addition, liver cyst infections in people with a prior kidney transplantation should be discussed in multidisciplinary teams to adjust antibiotic and immunosuppression drug levels where necessary.
Practice Point 5.3.2.4: 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 risk factors listed below and kept in place until drainage stops. In the case of deep cysts where percutaneous drainage is not feasible, surgical drainage may be necessary.

First-line therapy of infected liver cysts consists of antibiotics. A clinical response to antibiotics is expected within 48–72 hours and can be monitored with clinical parameters (i.e., temperature, BP, heart rate, and ventilation rate) in combination with laboratory evaluations (i.e., CRP and leukocyte count). A lack of response may be caused by several reasons. First, penetrance of the antibiotic into the liver cyst may be limited.\textsuperscript{452-454} Second, distribution of antibiotics within the cyst(s) may be difficult to achieve in large cysts or cysts with internal septa. Third, if a pathogen is resistant to the antibiotic, the infection will not be cleared. Finally, immunocompromised people have an increased risk for impaired pathogen clearance. If the person does not respond to antibiotic treatment, drainage of the cyst should be considered.\textsuperscript{451, 456, 459} If percutaneous drainage is not feasible, surgical drainage or partial liver resection may be used as alternative approaches.\textsuperscript{455, 456}

Practice Point 5.3.2.5: It may be reasonable to perform percutaneous drainage of infected liver cysts <48 hours after initiation of antibiotics in the presence of the following:

- Isolation of pathogens that are unresponsive to antibiotic therapy from a cyst aspirate,
- Immunocompromised people,
- Large infected hepatic cysts (>8 cm),
- Hemodynamic instability and/or signs of sepsis.

The presence of the risk factors outlined above predisposes a person to adverse outcomes with conventional antibiotic treatment. In these cases, therapeutic alternatives (percutaneous or surgical drainage) are needed.

Research recommendations

- Studies are needed to determine penetrance and drug levels of other antibiotics in infected and asymptomatic liver cysts.
- Studies are needed to determine the optimum treatment regimens for liver cyst infections.
- Studies are needed to determine the differences between liver and kidney cyst infections in terms of pathophysiology and treatment.
CHAPTER 6. INTRACRANIAL ANEURYSMS (ICA) AND OTHER EXTRARENAL MANIFESTATIONS

6.1. Intracranial aneurysms (ICA)
Recommendation 6.1.1: We recommend informing adults with ADPKD about increased risk for intracranial aneurysms (ICA) and subarachnoid hemorrhage (SAH; Figure 35) (IC).

ICA are acquired, pathological dilations at major branching brain arteries, which can remain stable, grow without or with subsequent rupture causing SAH, or rupture without prior ICA growth. This recommendation places a high value on the importance for the person to know their risk for ICA and SAH. This information allows for an open dialogue regarding preventive measures and awareness of possible symptoms of ICA rupture. The recommendation places a low value on the impact to the person’s QoL, such as anxiety or professional/personal choices that may be caused by knowing this information.

<table>
<thead>
<tr>
<th>Prevalence of ICA (95% CI)</th>
<th>General population</th>
<th>General population plus family history of ICA or SAH</th>
<th>ADPKD population</th>
<th>ADPKD population plus family history of ICA or SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2% (1.9–5.2)</td>
<td>4% (2.6–5.8)</td>
<td>11% (9–14)</td>
<td>12.9% (10.4–15.4) (Figure 36)</td>
<td>18% (13–24)</td>
</tr>
<tr>
<td>Incidence rates of SAH (per 1000 person-years, 95% CI)</td>
<td>0.079 (0.069–0.09)</td>
<td>3–7 higher risk</td>
<td>0.57 (0.19–1.14) (Figure 37)</td>
<td>Likely higher (based on data from general population)</td>
</tr>
</tbody>
</table>

Preventive screening for intracranial aneurysms. International journal of stroke: official journal of the International Stroke Society. 2022;17: 30-362. Box 7: See Figure 37

Key information

**Balance of benefits and harms**

Informing adults with ADPKD about their increased risk for ICA and SAH is a prerequisite to shared decision-making regarding screening for unruptured ICA. Information about ICA is also essential to open the discussion allowing clinicians to evaluate risk factors for ICA and SAH and to educate adults with ADPKD about prevention and specific symptoms that should prompt immediate medical evaluation. The Standardized Outcomes in Nephrology-Polycystic Kidney Disease (SONG-PKD) Consensus Study has highlighted that “cerebral aneurysms and stroke” were among of the main concerns of people with ADPKD. The benefits of this information substantially outweigh potential harms to the patients such as anxiety associated with this information.

Unruptured ICA are found in ~3.2% of the general population (mean age at screening 50 years) worldwide. ADPKD is associated with a 4-fold increased risk for developing ICA. However, the exact prevalence of unruptured ICAs in ADPKD is difficult to evaluate because their identification depends on the selection of people for imaging. Studies in ADPKD cohorts yielded prevalence estimates ranging from 9.2%–18.5% (Figure 36). Factors accounting for this heterogeneity include referral bias (i.e., some studies include people primarily from centers of expertise who may have a higher risk due to known family history), selection for screening (i.e., denominators may include only people who underwent imaging based on the existence of risk factors such as familial history), and ascertainment bias (e.g., people with undiagnosed ADPKD, who may be at lower risk of ICA, are not included). Most aneurysms detected by screening are small (<5 mm) and ~90% occur in the anterior circulation. Approximately 15%–25% of people with ADPKD who have an ICA have multiple ICA.

ICA rupture leading to SAH is associated with significant morbidity and mortality and, because ICA are more common in ADPKD, occurs more frequently in people affected by ADPKD than in the general population. Although the absolute aneurysm rupture rate in the ADPKD cohort is low, ~0.04 per 100 patient-years (95% CI: 0.01–0.06, Figure 37), nevertheless this is approximately 7 times higher than in the general population. The median age at aneurysm rupture is ~41 years in people affected by ADPKD versus 52 years in the general population.

**Certainty of evidence**

The certainty of evidence for estimates of both prevalence of ICA and incidence of ICA rupture in people with ADPKD was graded as low (Level C) due to both serious methodological limitations of the studies and inconsistency in estimates across studies (Supplementary Table S18). In most studies, the reasons or criteria for screening were unclear or variable among participants. The methods for diagnosing ICA or ICA rupture were highly variable across studies.
The certainty of evidence comparing risk of ICA rupture in people with ADPKD versus the general population was graded as moderate (Level B) due to serious methodological limitations of the studies (Supplementary Table S19). Although there was inconsistency (statistical heterogeneity) in the magnitude of the odds ratios comparing ADPKD versus general population, the studies were consistent in direction and strength of association. The study limitations are related to a lack of adjustment for potential confounders in most studies.

![Figure 36](image1.png)

**Figure 36. Incidences of new diagnosis of intracranial aneurysms (ICA) in people with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) at time of presymptomatic screening.**
- Percent of all people with ADPKD (without history of known ICA) who had imaging conducted.
- People with family history of ICA preferentially imaged (90% of such people, 21% of people with no family history of ICA).
- Screening of all people with ADPKD who agreed.
- Excluding people found to have subarachnoid hemorrhage (SAH) on imaging (it was not reported if these people had known or suspected ICA prior to imaging).
- No reason reported why imaging was conducted and number of people with known family history of ICA was not reported.
- People with known ICA (prior to imaging) excluded from this analysis (in contrast with numbers analyzed in article).
- No reason reported why imaging was conducted.

![Figure 37](image2.png)

**Figure 37. Incidence rate of ruptured ICA in people with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) at time of rupture.** CI, confidence interval; NR, not reported

**Values and preferences**

The Work Group judged that the majority of people with ADPKD would consider information about their increased risk of ICA and SAH as very important since it allows for open discussion about risk factors, screening, preventive measures (lifestyle), and symptoms that should trigger immediate medical attention. The Work Group also judged that it is important to
emphasize that although ICA are relatively frequent in people with ADPKD, the vast majority of ICA detected by screening will not rupture.

Resource use and costs

Informing people with ADPKD about their increased risk of ICA or SAH is important. It is anticipated that some people will want to be screened even if they are low risk.

Consideration for implementation

Figure 35 outlines the prevalence of unruptured ICA and the incidence of SAH rate in the general population and in people with ADPKD, overall or in the presence of a family history of SAH or ICA in a first degree relative. It is important to explain that although ICA are more frequently found in people with ADPKD than in the general population, a large majority of the ICA will not rupture and will remain asymptomatic.

Rationale

This recommendation stresses the importance of giving adequate information to people with ADPKD about their increased risk for ICA and SAH. While SAH is rare in people with ADPKD, this is the most severe extrarenal complication of ADPKD with potentially devastating consequences. People with ADPKD are often unaware of this increased risk, and in this case, may not inform their physicians about familial history of ICA, SAH, or sudden death, and may not recognize thunderclap headache. A survey amongst 420 nephrologists from France, Belgium, and Switzerland showed that when the nephrologists considered that screening was not indicated, only 35% would still systematically inform the person about the risk of ICA and SAH, 53% would give information on a case-by-case basis according to their evaluation of the person’s demand, and 12% would not give information at all.475

Practice Point 6.1.1. All people with ADPKD should be educated to recognize thunderclap headache which should prompt immediate medical attention.

Thunderclap headache or sentinel headache refers to a severe headache of sudden onset, typically reaching its maximum intensity within ≤1 minute of onset. SAH is a frequent cause of a thunderclap headache and should be of particular concern in the context of ADPKD. Thunderclap headaches should be investigated emergently to enable prompt treatment of a possible SAH.

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 at higher risk for ICA.

Practice Point 6.1.3: Because tobacco exposure is a strong modifiable factor for ICA development and rupture, clinicians 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 strong 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 in those at an increased risk for ICA (Chapter 2).

Nonmodifiable and modifiable risk factors of ICA development or rupture are listed in Table 12. Nonmodifiable factors include female sex, older age, personal history of prior SAH or ICA, family history of SAH or ICA, and possibly PKD1 pathogenic variants and severity of the polycystic kidney disease. As observed in the population without ADPKD, women have a higher risk of ICA and SAH, especially after 50 years of age.\textsuperscript{460, 476} In people with ADPKD and a positive family history of SAH or ICA, the risk for ICA is 4 times higher than in those with no such familial history.\textsuperscript{477} Some studies have suggested an association between the severity of ADPKD (reflected by TKV, MIC 1D–1E, and severity of CKD G3–G5) with ICA formation.\textsuperscript{467, 469}

<table>
<thead>
<tr>
<th>Predictors for prevalent ICA or rupture of ICA and strength of the association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence for association with ICA/SAH in ADPKD population</td>
</tr>
<tr>
<td>• Family history of SAH or ICA (stronger association when first-degree relative) – Strong</td>
</tr>
<tr>
<td>• Personal history of SAH or ICA – Strong</td>
</tr>
<tr>
<td>• Female sex – Moderate</td>
</tr>
<tr>
<td>• PKD1 genotype – Moderate</td>
</tr>
<tr>
<td>• Tobacco smoking (especially &gt;20 pack-years) – Strong</td>
</tr>
<tr>
<td>• Uncontrolled hypertension – Moderate</td>
</tr>
<tr>
<td>• Early onset hypertension (&lt;35y) – Moderate</td>
</tr>
<tr>
<td>• Severity of ADPKD – Weak</td>
</tr>
<tr>
<td>Evidence in non-ADPKD population</td>
</tr>
<tr>
<td>• Japanese or Finnish ancestry</td>
</tr>
<tr>
<td>• Alcohol in large quantity (risk factor for ICA rupture)</td>
</tr>
</tbody>
</table>

Table 12. Risk factors of intracranial aneurysms (ICA) or subarachnoid hemorrhage (SAH). ADPKD, autosomal dominant polycystic kidney disease

No genetic determinants of ICA formation and development have been identified up to now in ADPKD. People with PKD1 pathogenic variants appear to have a higher risk of diagnosis of ICA and SAH than people with PKD2.\textsuperscript{476} However, the role of confounding factors cannot be excluded. First, early ICA rupture, before the diagnosis of ADPKD, might occur in some PKD2 pathogenic variant carriers; and second, screening for ICA might be more frequently conducted in PKD1 pathogenic variant carriers, who generally have more severe kidney disease, resulting in an earlier ADPKD diagnosis and closer medical follow-up. No specific PKD1 pathogenic variant has been associated with an increased risk for ICA.\textsuperscript{476} Former studies reported people with ICA in unrelated families harboring a 2 base-pair deletion in PKD1 (c.5014_5015delAG), suggesting an association with this specific mutation, but more systematic genetic testing in people with ADPKD has now established that this variant is in fact the most common pathogenic variant of PKD1 (~1–2%).\textsuperscript{478} While a study from the early 2000s suggested an association
between *PKD1* variant position and ICA, neither pathogenic variants localization nor variant type (i.e., truncating versus nontruncating) were found to be associated with diagnosis of ICA or SAH in a larger and more recent study.\textsuperscript{476, 479}

Modifiable factors of ICA development or rupture include tobacco smoking and hypertension.\textsuperscript{462, 463, 476} In a cross-sectional study led in the Genkyst cohort, including ~2500 people with ADPKD, past or active smoking over 20 pack-years and hypertension were both independently associated with a 2-fold increased risk of ICA and SAH, after multivariate adjustment.\textsuperscript{476} In a study conducted in the Mayo Clinic cohort, hypertension and smoking history were significantly more frequent in people with ADPKD with ICAs than in people with ADPKD without ICAs (43\% vs. 23\% and 90\% vs. 77\%, respectively).\textsuperscript{462, 476} Smoking prevalence varies widely among countries; for example the age-standardized smoking prevalence for both sexes combined in 2012 was 31.0\% in France compared to 15.8\% in the U.S.. This may also contribute to differences in the prevalence of ICA and incidence of SAH among countries. Excessive alcohol intake has been associated with an increased risk for SAH in the general population, but this association has not been explored in people affected by ADPKD.\textsuperscript{480}

In the general population, global SAH incidence declined from 10.2 (95\% CI: 8.4–12.5) per 100,000 person-years in 1980 to 6.1 (95\% CI: 4.9–7.5) in 2010, or by 1.7\% (95\% CI: 0.6–2.8) annually between 1955 and 2014, in parallel with a decrease in BP and smoking.\textsuperscript{461, 464} In Finland, the incidence of SAH decreased 24\% from 11.7 in 1998–2000 to 8.9 per 100,000 persons in 2010–2012, at the same time that daily smoking decreased 30\% between 1998 and 2012.\textsuperscript{481} Whether the incidence of SAH has continued to decline in the last decade and whether a similar decline has been observed in people with ADPKD is not known. Nevertheless, 2 of 29 deaths among 56 people with ADPKD during 1935–1980, but none of 21 deaths among 129 people with ADPKD during 1980–2016 in Olmsted County, Minnesota were due to a ruptured ICA.\textsuperscript{482, 483} The general populations in Japan and Finland have been reported to have a higher risk of ICA and SAH than other populations.\textsuperscript{484–486} Whether this higher prevalence also applies to people with ADPKD is currently unknown. However, 2 single-center studies in Japan reported prevalence of ICA of 17.6\% and 20.1\%, which is higher than in other ADPKD cohorts.\textsuperscript{469, 487} Whether other national, ethnic, or cultural general populations are also at higher (or lower) risk of ICA and SAH is unknown.

Limited data are available to assess the risk of rupture of ICA in the ADPKD population. A North American prospective study led in 1692 people without ADPKD with unruptured ICA reported that the strongest predictors of rupture were aneurysm size, location (posterior circulation and posterior communicating artery), and previous SAH.\textsuperscript{488} Parallel observations were made in a study from Japan including 6697 people with SAH highlighting the role of ICA size (≥7 mm), location (anterior and posterior communicating arteries), and the presence of a daughter sac to predict ICA rupture.\textsuperscript{489} The prognostic scoring system called PHASES (Population, Height, Age, Size of aneurysm, Earlier subarachnoid hemorrhage from another aneurysm, Site of aneurysm) was developed from 6 prospective studies, and allows evaluating
the 5-year rupture risk based on the 6 factors in its acronym.\textsuperscript{484} There is currently no supporting data to use the PHASES score in people with ADPKD.

**Practice Point 6.1.5. People should be informed of the implications of ICA screening as highlighted in Table 13.**

Comprehensive information should be given by the physician prescribing cerebral imaging before ordering a test. Adequate time should be given to the patient for informed decision-making.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May allow adequate intervention if an ICA at risk of rupture is identified, allowing to prevent death or significant comorbidity.</td>
<td>• Likely to identify ICA with very low risk of rupture ($\leq$5 mm/anterior circulation) and which do not require intervention but require long-term follow-up</td>
</tr>
<tr>
<td>• May reduce anxiety and provide reassurance when no ICA is detected</td>
<td>• Does not exclude the risk of \textit{de novo} ICA development and rupture after screening</td>
</tr>
<tr>
<td></td>
<td>• May lead to procedures with possible treatment failure or complications, including death or significant morbidity</td>
</tr>
<tr>
<td></td>
<td>• May cause anxiety when an ICA is identified</td>
</tr>
<tr>
<td></td>
<td>• May limit access to life insurance, loans, or driving licenses</td>
</tr>
<tr>
<td></td>
<td>• May limit work opportunities</td>
</tr>
<tr>
<td></td>
<td>• Cost associated with screening</td>
</tr>
</tbody>
</table>

*Table 13. Advantages and limitations of screening for unruptured intracranial aneurysms (ICA).*

**Recommendation 6.1.2. We recommend screening for ICA in people with a personal history of SAH or a positive family history of ICA, SAH, or unexplained sudden death if the person will be eligible for treatment and has reasonable life expectancy ($ID$).**

*This recommendation places a high value on the increased prevalence of ICA and the associated increased incidence of SAH in this population and the available options to treat or prevent an ICA rupture. Additionally, screening in this population may rule out the presence of an ICA, but not the possibility of future development, and may provide reassurance to the person. The recommendation places a lower value on the limitations of screening for unruptured ICA as listed in Table 13, as well as the potential harms of procedures when an ICA is found or the anxiety of knowing about an ICA.*

**Key information**

*Balance of benefits and harms*
The frequency of ICA in people with a positive family history of SAH or ICA undergoing screening is ~20%–30%. The probability of identifying an ICA is ~4 times higher than in people with ADPKD overall, and appears maximal in case of positive family history of SAH in a first-degree relative and in case of ICA/SAH in 2 relatives or more. It should be also noted, however, that 50%–60% of the people with ADPKD and diagnosed with ICA, and ~40% of those with ruptured ICA, do not have any familial history of ICA/SAH.

The rupture of an ICA is a devastating event, with a mortality rate >30%, and a morbidity rate of 50% (including neurocognitive dysfunction, epilepsy, and other focal neurologic deficits). The outcomes of ICA ruptures in people with ADPKD does not differ from those of matched people without ADPKD with aneurysmal SAH. At 12 months, 75% and 71% of the people with and without ADPKD with ICA ruptures admitted to neurointensive care units in Kuopio, Finland, had good outcomes (Glasgow Outcome Scale Score 4 or 5). Screening for unruptured ICA in people at high risk may allow adequate intervention if an ICA at risk of rupture is identified, preventing significant morbidity and/or death. In people at high risk, a negative screen can be reassuring.

The incidence of ruptured ICA from a meta-analysis of 5 studies in populations of different national and ethnic background is presented in Figure 37. Among people with ICA found on imaging and subsequent imaging surveillance, the incidence rate of aneurysmal SAH was 1.21 (95% CI: 0.17–8.53) (Figure 38). In people with no ICA found on imaging, the incidence rate was significantly lower at 0.39 (95% CI: 0.1–0.89) (Figure 38). In 2 studies that provided follow-up information on individuals with ADPKD who received preventive treatment for an ICA detected through screening, there were no reported cases of rupture.

![Figure 38. Incidence rate of ruptured ICA in ADPKD-affected people with a diagnosis of intracranial aneurysm and under imaging surveillance, and in ADPKD-affected people in whom no ICA were detected on imaging. CI, confidence interval; NR, not reported](image)

Possible limitations of screening for ICA are listed in Table 13. These include treatment failure, the risk of complications in case of preventive treatment of an ICA found at screening (i.e., peri-procedural stroke, death), and the need for long-term follow-up to detect recurrence or de novo aneurysm formation. A meta-analysis of 114 studies of 106,433 people from the general population found a pooled clinical complication risk within 30 days of 4.96% (95% CI: 4.0%–6.1%) and a clinical fatality risk of 0.3% (95% CI: 0.2%–0.4%) for endovascular treatment (74
studies). For neurosurgical treatment, the pooled clinical complication risk was 8.3% (95% CI: 6.3%–11.1%) and the clinical fatality risk 0.1% (95% CI: 0.0%–0.2%) (54 studies). There is also a risk of finding an ICA that is too small to be treated and must be followed up for possible growth, a situation that may cause anxiety, affect QoL, and may limit access to life insurances, loans, or driving license. Despite these limitations, which should be clearly discussed with the patient prior to ordering imaging, this Work Group felt that the advantages of screening in people at high risk outweigh the disadvantages.

**Certainty of evidence**

The certainty of evidence is very low (Level D) regarding benefits and harms of ICA imaging (versus not imaging) in people with increased risk of ICA rupture (Supplementary Table S20). One study with serious limitations provided highly imprecise estimates of risk of death and ICA rupture, but the study compared people with a family history of ICA who had imaging versus people without a known family history of ICA who did not have imaging.

**Values and preferences**

Because of the high prevalence of ICA among people with a personal history for SAH or a positive familial history for ICA, there was a strong consensus in the Work Group to recommend screening in this group of people. The Work Group judged that the majority of people would want to know their diagnosis with regard to ICA. When familial history is not available, when ADPKD occurs de novo or when cause of sudden death is unclear in a relative affected by ADPKD, suggestions for screening appear appropriate as familial risk for ICA cannot be precisely evaluated. The Work Group judged that it was important to mention that screening for ICA should only be performed in people with a reasonable life expectancy and eligible to treatment in case of identification of an ICA at risk for rupture.

**Resource use and costs**

The cost associated with screening (i.e., computed tomography angiography [CTA] or magnetic resonance angiography [MRA]) may limit its accessibility in low-resource areas or in countries without universal healthcare. Two studies suggested that screening all people with ADPKD for ICA may be cost-effective as compared to targeted screening or to no screening. Cost-effectiveness is increased in populations with a higher pretest probability of having an ICA, therefore, although we do not have the specific estimates in this subgroup of people, screening for ICA in people with a personal history of SAH or a familial history of ICA/SAH is deemed to be cost-effective as compared with no screening.

**Consideration for implementation**

ICA rupture is an exceedingly rare phenomenon in children; it is therefore not indicated to start screening before adulthood. In rare cases with a positive family history of early rupture and a strong desire to ease anxiety by screening, an individualized approach is justified. The individual candidates for screening should be informed that if an ICA is identified on screening, their relatives affected with ADPKD (particularly his/her first-degree relatives >18 years) may also become eligible for screening. People should also be informed that there is a
chance of incidental findings other than ICA, notably including asymptomatic brain infarctions, meningioma, arachnoid cysts, or hypophyseal adenoma.\textsuperscript{461}

**Rationale**

We make this recommendation considering the increased risk for ICA and SAH in people with ADPKD and a positive familial history of ICA and SAH, as well as the available options to treat or prevent an ICA rupture. Given the disadvantages associated with screening, people should be counseled before imaging. Current treatment strategies for preventive aneurysm occlusion carry a \(5\%–8\%\) complication risk which reduces the benefit of screening. If noninvasive strategies to reduce the risk of development or rupture of ICA become available (e.g., pharmacological treatment), this recommendation will likely evolve towards more systematic screening.

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

**Practice Point 6.1.7.** Screening for unruptured ICA may also be considered 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.

The potential benefit of screening for unruptured ICA in people with ADPKD depends on the prevalence of ICA, the risk of rupture with medical therapy alone, the rate of complications associated with strategies employed for preventive occlusion of the aneurysm as well as their technical success, and the risk of *de novo* aneurysm development and rupture. In any case, people should be adequately informed on the potential implications of detecting an intracranial finding on imaging (e.g., future obtainment of life insurance), as well as anxiety that can be associated with ICA detection, notably when preventive occlusion is not indicated.

A cost-effectiveness study conducted in 495 consecutive people with ADPKD from a single center in France concluded that systematic screening was deemed cost-effective, providing a gain of 0.68 quality-adjusted life years compared to targeted screening.\textsuperscript{466} However, the aneurysm rupture rate in this study was 5 times higher than in other ADPKD cohorts, potentially limiting the generalizability of the findings until replicated by other centers. While there is a strong consensus to recommend screening in people with a positive family history of SAH or ICA in a first-degree relative, screening is also discussed in other situations depending on countries and centers, such as during pretransplant evaluation or before major elective surgery.
Moreover, screening for unruptured ICA is sometimes required by occupational health services, for instance in people who work in high-risk occupations (e.g., bus drivers, airline pilots) in whom loss of consciousness from a ruptured aneurysm would place the lives of others at risk.

Current treatment strategies for preventive aneurysm occlusion are associated with a significant risk for complication, which reduces the benefit of screening. Two studies reported higher complication rates associated with cerebral angiography or treatment of unruptured ICAs in people with ADPKD compared to people without ADPKD. The first study described transient complications of cerebral angiography (carotid artery vasospasm, severe headache, scotomata, vertebral artery dissection) in 8 of 32 (25%) people with ADPKD compared to 22 of 220 (10%) people without ADPKD. The high rate of complication has to be interpreted in the context of the study period (1985–1990) as the risk of complication of preventive aneurysm occlusion has decreased over the last decades. The second study described more frequent complications after endovascular coiling (hemorrhage or infarction, embolic infarction, and carotid artery dissection) or surgical clipping (hemorrhage, infarction) in people with ADPKD compared to people without ADPKD (9.4% and 11.8% vs. 3.0% and 6.4%, respectively). If noninvasive treatment strategies, such as medical treatment, to reduce the risk of rupture of unruptured ICA become available, the groups of people in whom screening would be advised would increase considerably. However, beyond the situations listed above, despite not being considered “at increased risk”, some people with ADPKD may be in favor of screening for ICA after having received comprehensive information and should be given access to screening.

Practice Point 6.1.9: Time-of-flight (TOF) 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 an alternative.

MRA and CTA appear to be able to detect aneurysms ≥5 mm; smaller aneurysms (down to 2 mm) are less reliably detected or may be seen in retrospect when compared with digital subtracted angiography (DSA). CTA can be considered as an initial diagnostic test for aneurysm detection and screening. However, exposure to iodine contrast can be associated with degradation of kidney function, especially in people with eGFR < 30 ml/min per 1.73 m² and can cause rare allergic reactions. Exposure to radiation can be a concern in people undergoing multiple evaluations. Besides, CTA may be limited by artifact from bone and metal (coils, stents, and clips), thereby reducing its usefulness in people with previously treated ICA.

Imaging aneurysms with MRA typically uses TOF method, and GBCA are not required. In the absence of contraindications (i.e., metallic foreign bodies, implants, external devices/accessory medical devices), MRA is a safe diagnosis procedure. Some people may, however, experience claustrophobia.
While DSA is still considered as the “gold-standard” and is highly sensitive especially for aneurysms <3 mm, noninvasive imaging should be favored to avoid the risks associated with catheter arteriography, including contrast-related events (e.g., allergy, AKI), cerebral infarction, aneurysm rupture, and arterial injuries.

There is no head-to-head comparison of performances of MRA versus CTA versus DSA in people with ADPKD, and the evidence considered here is derived from studies in the general population. CTA sensitivity and specificity to detect small ICA (3–5 mm) were estimated to be 95%–97% and 100%, respectively, while for ICA<3 mm sensitivity was lower (84%–86%) without loss of specificity. TOF MRA has a detection sensitivity ranging from 74%–98%. ICA size again greatly affects the results; however for small aneurysms (≤3 mm), the sensitivity of TOF MRA at 3.0 Tesla (T) is >95%.

Although CTA and MRA do have similar sensitivities to detect aneurysms >3 mm, the Work Group judged that the majority of people would choose MRA as the screening method of choice, as it allows to limit exposure to radiations and iodine-contrast, particularly in people with an eGFR <30 ml/min per 1.73 m². CTA also has a high diagnosis accuracy and is a valid alternative, when MRA is not available or when there are contraindications to MRA. DSA is associated with risks for complications, albeit rare, and for this reason it should not be used in the setting of pre-symptomatic screening.

The financial burden or the limited availability of MRA in some areas may limit access to MRA as a first-line imaging. In the absence of contraindication, CTA can be considered as an initial diagnostic test for screening and remains more accessible than MRA in several countries or areas. In case of equivocal results from a first imaging, another technique may occasionally be needed (i.e., MRA with a 3.0 T magnet needed after the identification of an image compatible with a small-sized ICA visualized on a 1.5 T MRA or on a CTA), increasing the screening cost.

Contraindications for MRA (i.e., presence of cardiac implantable electronic device, metallic intraocular foreign bodies, metallic fragments, cerebral artery aneurysm clips [although most clips are now compatible]) should be carefully reviewed and people should be asked if they have a history of claustrophobia before prescribing an MRA. Contraindication for CTA (e.g., allergy to iodine, eGFR<30 ml/min per 1.73 m², pregnancy) should also be reviewed.

Practice Point 6.1.10: If the screening is negative in people with high-risk of ICA, timing of rescreening should be individualized based on risk factors, age, and life expectancy.

There is limited evidence to define an optimal interval for repeated imaging (MRA or CTA) among people who do not have an aneurysm detected on initial imaging but have a family history of ICA. In one study including 76 people with ADPKD and initial negative MRA, 2 people developed an ICA on rescreening after 10 years. In another study, among 135 people with initial negative MRA and follow-up MRA available, 3 developed an ICA on rescreening after a median follow-up of 7.4 years, while among 734 people with initial negative MRA and
clinical follow-up available, 2 people, both with positive family histories, had a ruptured aneurysm.\textsuperscript{462} Based on this limited evidence, 5–10-year intervals are generally suggested, but should be discussed and individualized according to family history of SAH, life expectancy, possibility of intervention in case of positive screen, risk factors (i.e., number of affected relatives with ICA/SAH, tobacco use, uncontrolled hypertension). It is important to note that despite repeated screening and preventive treatment of unruptured ICAs, not all episodes of SAH can be prevented. In rare instances, ICA can develop and rupture within the regular screening interval of 5 years, or a very small ICA (that would not have been treated) can rupture.\textsuperscript{466, 506} The role of repeat imaging among those with negative imaging but without a family history is less clear and should be discussed on a case-by-case basis after careful discussion of the benefits and harms of screening highlighted in Table 13.

**Practice Point 6.1.11:** 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.

Limited information on the natural history of ICAs in people with ADPKD is available, and as previously mentioned, there are currently no predictive tools to evaluate the risk of rupture of ICA in these people. In an observational study from the Mayo Clinic, including 38 people with unruptured saccular ICAs detected during screening, no ICA rupture was reported during a median follow-up of 7.9 years.\textsuperscript{477} In a follow-up study from the same group, including 75 people with unruptured ICAs detected during screening and follow-up MRAs, no ICA rupture was reported. ICA growth was detected in 13\% of the cases during a median follow-up of 6 years with an average increase of ICA diameter of 2 mm. \textit{De novo} ICA measuring $\geq$2 mm were also detected in 5 people.\textsuperscript{462} These studies suggest that the risk of rapid expansion or rupture of small, unruptured ICAs detected by screening in people with ADPKD is quite low.

Decisions regarding the management of ICA should be assessed in a multidisciplinary setting including experienced radiologists, neurosurgeons, and neuro-interventional radiologists. Key factors taken into account both for the decision to intervene and the choice of intervention are the general health and life expectancy of the affected individual; the size, shape, and location of the ICA; the growth of ICA when follow-up imaging are available; the risk factors for rupture (history of SAH, smoking, and hypertension); and the estimated risk of treatment (comorbid disease, ICA morphology).\textsuperscript{507} The recent European guideline on the management of unruptured ICA does not provide general recommendation stating which treatment modality (endovascular vs. microsurgical) is preferred but insists on the importance that therapeutic decisions and treatments should be made in centers of expertise with high ICA case volumes.\textsuperscript{507} For ICA occurring in the posterior circulation, endovascular treatment is recommended as the first option to consider.\textsuperscript{507}

In people with unruptured ICA with no indication for treatment, radiological monitoring to detect ICA growth, morphological modification and/or \textit{de novo} ICA should be continued as long as preventive treatment remains an option.\textsuperscript{507} The frequency of MRA or CTA is
individualized based on ICA and patient-related risk factors for rupture and usually varies from 6 months initially to 1–2-year intervals.\textsuperscript{497}

### 6.2. Other vascular associations

**Practice Point 6.2.1:** There is no role for routine screening of vascular abnormalities of nonintracranial large arteries in people with ADPKD and no familial history of vascular aneurysms or dissections.

Dilatation and dissection of nonintracranial large arteries (thoracic aorta, coronary, cervicocephalic, vertebral) have been described in people with ADPKD.\textsuperscript{508, 509} Because the majority are sporadic cases, routine screening is not indicated. Aortic aneurysms are discussed in Practice Point 6.2.2. Several cases of coronary artery dissection have been reported to date, as well as fewer cases of vertebral and carotid artery dissection.\textsuperscript{510-518} Although the number of reported cases is limited, the broad range of vascular abnormalities observed in ADPKD, including arterial aneurysms and dissections, suggest that people with ADPKD may be at increased risk for thoracic aortic, carotid, vertebral, and coronary artery dissections.

**Practice Point 6.2.2:** In case of familial history of aortic root or thoracic aortic aneurysms in people with ADPKD, screening of first-degree relatives should be performed.

Whether ADPKD is associated with an increased risk for abdominal aorta aneurysms (AAA) is uncertain. A single-center study from Spain enrolling 139 people with ADPKD (76 were >40 years of age) and 149 family members without ADPKD showed similar abdominal aortic diameters in both groups across all age groups.\textsuperscript{519} A population-based cohort study from the Taiwan National Health Insurance Research Database reported a ~5-fold greater risk for aortic aneurysms and dissection occurrence in people affected by ADPKD as compared to non-ADPKD counterparts. This increased risk appeared to be driven by increased occurrence of thoracic aortic aneurysm (TAA), which was highest in people with ADPKD and hypertension.\textsuperscript{520}

Several case reports and case series of people with ADPKD and TAA, including aortic root dilatation, TAA of the aortic arch, and TAA of the descending aorta have been reported to date.\textsuperscript{521-524} Familial clustering of TAA in people with ADPKD has occasionally been reported.\textsuperscript{525, 526} A retrospective single-center study comparing diameters of the ascending aorta in people with ADPKD and matched controls found significantly higher diameters of the sinuses of Valsalva (SoV) and Z-scores (normalized for sex, age, and body surface area) both for SoV and tubular ascending aorta in those with ADPKD.\textsuperscript{247}

While specific studies to assess the familial risk for TAA in ADPKD are lacking, in the population without ADPKD, up to 20\% of people with a TAA were found to have another first-degree relative with TAA.\textsuperscript{527, 528} For this reason, screening of first-degree relatives should be considered in case of diagnosis of TAA.
In people eligible for screening (e.g., first-degree relatives of a person with a diagnosis of TAA), contrast-enhanced CT scan or MRA can be performed. Transthoracic echocardiography is a standard approach to identify and monitor aortic root dilatation.

**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 include smoking cessation, statin therapy, and antihypertensive therapy including a beta-blocker and ACEi or ARB.

There are no specific studies in the ADPKD population, and most trials have focused on cohorts of people with either Marfan syndrome or AAA. Uncontrolled hypertension increases the risk for aortic dissection;\(^{529}\) therefore, achieving BP target as detailed in Chapter 2 can reduce adverse clinical outcomes. The most robust evidence of antihypertensive therapy in AAA is for beta-blockers and RASi.\(^ {529}\) Although mostly studied in the context of AAA, statin therapy may provide a protective effect by targeting inflammatory and atherosclerotic pathways.\(^ {529}\)

Fluoroquinolones have been linked to an increased risk of aortic dissection and aneurysm rupture, but the magnitude of this effect varies across studies and the pathways through which this effect is mediated are unknown; therefore, future research is needed to elucidate the potentially protective or harmful effect of pharmacologic agents.\(^ {530-532}\)

**6.3. Cardiac associations**

**Practice Point 6.3.1:** There is no role for routine baseline or surveillance echocardiography in people with ADPKD without signs or symptoms of cardiac dysfunction, heart murmur, or other cardiovascular manifestations.

Valvular abnormalities of unclear clinical significance, including mitral valve prolapse (MVP) and aortic regurgitation, can be detected by echocardiography in people with ADPKD.\(^ {248, 533}\) MVP was formerly reported to be present in 20%–30% of the people with ADPKD, but more recent studies using current definition of MVP reported prevalence of 1% in pediatric and 3.4% in adult cohorts, similar to that in the general population.\(^ {534, 535}\) Most people with valvular disease are asymptomatic and many will not have an audible murmur. Some studies suggest that primary cardiomyopathies (e.g., dilated, hypertrophic, and left ventricular noncompaction) and atrial fibrillation may be more common among people with ADPKD compared with the general population.\(^ {536, 537}\) While there is no evidence to recommend routine presymptomatic echocardiography in all people with ADPKD, it should be performed in those with a positive family history of 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, especially in people with kidney and/or liver enlargement.

Practice Point 6.4.2: People with ADPKD 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 could be considered in people with ADPKD who elect PD as a mode of KRT, since increased abdominal pressure is a known risk factor for enlargement and complications of hernias.

While there is limited published evidence in the literature describing an increased risk for abdominal wall hernias in ADPKD, there was a strong consensus in the Work Group to describe abdominal wall hernias as a common clinical situation in people with ADPKD. Published evidence mostly included people with ADPKD and kidney failure, therefore are more likely to have enlarged kidneys (and/or liver). One study reported higher prevalence of abdominal wall hernias in people with kidney failure due to ADPKD compared with age and sex matched controls with kidney failure due to other etiologies (45% vs. 16%), and that the difference was significant for inguinal, incisional, and paraumbilical. Interestingly, 18 people were diagnosed before the detection of kidney disease, suggesting that nephromegaly is not the only driver of the development of hernia. Another study describes a higher incidence of inguinal hernia in people with ADPKD receiving PD when compared to people without ADPKD undergoing PD. A meta-analysis showed that the risks of abdominal hernia were higher in people with ADPKD undergoing PD than in other etiologies of kidney failure (Chapter 3). Abdominal wall hernias in ADPKD likely result from the combination of altered matrix integrity and increased abdominal pressure from cyst burden. Complications of surgical management of abdominal wall hernia in people with ADPKD include poor wound healing, infectious complications including cysts infection, and recurrence of hernia. Therefore, in people with severely enlarged kidneys and/or liver, abdominal wall hernia should be managed expectantly whenever possible, and people should be educated to recognize signs of acute complication such as incarceration or strangulation. Surgical repair in people with CKD G5 opting for PD is generally performed before or at the time of catheter insertion. Feasibility of PD in people with massive kidney and/or liver enlargement and abdominal wall hernia should be carefully evaluated before surgical repair (see also Chapter 3).

Indication for surgical treatments varies also according to the site of hernias. Femoral hernias are associated with a higher risk of developing complications than inguinal hernias, and hence surgical repair rather than watchful waiting, is usually suggested. People should also be counseled about modifiable risk factors, including smoking cessation, medical optimization (e.g., diabetes), and weight loss when indicated.

6.5. Other extrarenal manifestations
Table 14. outlines some of the central nervous system, cardiovascular, hepatic, gastrointestinal, and other extrarenal manifestations of ADPKD. The table also provides the proportion of people with ADPKD for each category and guidance for screening.
### Extrarenal manifestations described in ADPKD

#### Central nervous system manifestations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimation of the % of people affected by ADPKD</th>
<th>Details or notes</th>
<th>Guidance for imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial aneurysm</td>
<td>Summary: 11.9% (95% CI: 7.6–16.2) [Range across studies 4.7%–20.1%]</td>
<td>Prevalence in ADPKD population is difficult to assess because systematic screening is usually not performed</td>
<td>See Recommendation 6.1.2. and Practice Point 6.1.6</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>Summary: 1.3% (95% CI: 0.6–2.3) [Range across studies 0.07%–3.0%]</td>
<td>Thunderclap headache should lead to immediate medical attention</td>
<td>Only if there are symptoms</td>
</tr>
<tr>
<td>Intracranial arterial dolichoectasia</td>
<td>~0.7%–5%</td>
<td>Dolichoectasia (dilatative arteriopathy) is usually asymptomatic, but may cause stroke, and may mimic ICA on imaging studies.</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Arachnoid cyst</td>
<td>8%–15%</td>
<td>Usually asymptomatic, incidental diagnosis. Possible increased risk of spontaneous subdural hematoma</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Meningeal cyst</td>
<td>Rare case reports</td>
<td>Usually asymptomatic, incidental diagnosis. May very rarely cause spontaneous intracranial hypotension</td>
<td>No systematic screening</td>
</tr>
</tbody>
</table>

#### Cardiovascular manifestations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimation of the % of people affected by ADPKD</th>
<th>Details or notes</th>
<th>Guidance for imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve prolapse and regurgitation</td>
<td>MVP 3%–26%</td>
<td>Usually asymptomatic. MVP was formerly reported to be present in 20%–30% of people with ADPKD, but more recent studies using current definition of MVP reported prevalence of 1% in pediatric and 3.4% in adult cohorts, similar to the general population.</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>~20%</td>
<td>Usually asymptomatic, incidental diagnosis</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>~8%</td>
<td>Hypertrophic cardiomyopathy: 2.5%* Dilated cardiomyopathy: 5.8%*</td>
<td>No systematic screening</td>
</tr>
</tbody>
</table>

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223
<table>
<thead>
<tr>
<th>Extrarenal manifestations described in ADPKD</th>
<th>Estimation of the % of people affected by ADPKD</th>
<th>Details or notes</th>
<th>Guidance for imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart malformation</td>
<td>&lt;2%</td>
<td>Left ventricular noncompaction: 0.3% Very rare case-series and case reports</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Situs inversus and large vessels transposition</td>
<td>Rare case reports</td>
<td>Laterality defects including dextrocardia and situs inversus totalis have been reported in a small number of people with ADPKD, mostly PKD2 (genetic testing was not performed in all reported cases)</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Thoracic aortic aneurysm</td>
<td>~1.5%</td>
<td>See Practice Point 6.2.2</td>
<td>No systematic screening. To be considered in case of positive familial history</td>
</tr>
<tr>
<td>Thoracic aortic dissection</td>
<td>Very rare case reports</td>
<td>Acute abdominal pain is present in &gt;90% of the cases. People generally present with symptoms and signs characteristic of acute myocardial infarction. Usually young, and more frequent in women</td>
<td>Only if there are symptoms</td>
</tr>
<tr>
<td>Coronary arteries dissection</td>
<td>Very rare case reports</td>
<td>People generally present with symptoms and signs characteristic of acute myocardial infarction. Usually young, and more frequent in women</td>
<td>Only if there are symptoms</td>
</tr>
<tr>
<td>Carotid and vertebral artery dissection</td>
<td>Very rare case reports</td>
<td>Often result in ischemic stroke or transient ischemic attack, often associated with neck pain or headaches. Occasional Horner syndrome in case of carotid dissections</td>
<td>Only if there are symptoms</td>
</tr>
<tr>
<td>Retinal artery and vein occlusion</td>
<td>Very rare</td>
<td>Single case-series of 8 people with ADPKD</td>
<td>No systematic screening</td>
</tr>
</tbody>
</table>

**Hepatic and gastrointestinal manifestations**

224
<table>
<thead>
<tr>
<th>Extrarenal manifestations described in ADPKD</th>
<th>Estimation of the % of people affected by ADPKD</th>
<th>Details or notes</th>
<th>Guidance for imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic polycystic liver disease</td>
<td>&lt;5% predominant in females</td>
<td>Liver cysts are present in &gt;80% by age 30 years</td>
<td>Include liver imaging in initial visit (Chapter 5)</td>
</tr>
<tr>
<td>Congenital hepatic fibrosis</td>
<td>Very rare case reports</td>
<td>More common in ARPKD</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Pancreatic cysts and IPMN</td>
<td>Pancreatic cysts ~10%</td>
<td>Any complex pancreatic cyst or in case of multiple cysts should be followed and evaluated to exclude malignancy</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Splenic cysts</td>
<td>~7%</td>
<td>Like general population. Usually asymptomatic, incidental diagnosis.</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Abdominal wall hernia</td>
<td>Common</td>
<td>Published evidence from a small cohort in Wales but very common clinical finding</td>
<td>Clinical examination</td>
</tr>
<tr>
<td>Dilated extrahepatic bile duct</td>
<td>~40%</td>
<td>Small cohort single study</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Colonic diverticulosis</td>
<td>1.5% of all people with ADPKD (vs. 0.8% of general population; adjusted OR: 1.88; 95% CI: 1.82–1.93) 2.6% of people with kidney transplant and ADPKD (vs. 0.8% of people with kidney transplant without ADPKD)</td>
<td>Single, large national database.</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Duodenal or small bowel diverticula</td>
<td>Rare case reports</td>
<td>Rarely, periampullary duodenal diverticula may be associated with obstructive jaundice or ascending cholangitis. Small bowel diverticula may be associated with bacterial overgrowth</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Extrarenal manifestations described in ADPKD</td>
<td>Estimation of the % of people affected by ADPKD</td>
<td>Details or notes</td>
<td>Guidance for imaging</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Bronchiectasis</td>
<td>19%–37%</td>
<td>Incidental radiology finding typically of no clinical significance</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>21% vs. 8% in controls</td>
<td>Incidental finding, more frequent in females, not clinically significant</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Sperm abnormality</td>
<td>Abnormal semen parameters reported</td>
<td>May be associated with male infertility although no large study has demonstrated that male infertility was more common in ADPKD</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Seminal vesicle cysts</td>
<td>20%–40%</td>
<td>Although commonly identified, seminal vesicle cysts do not result in male infertility</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Seminal vesicle ectasia</td>
<td>Ectasia &gt;10 mm: 23%</td>
<td>Although commonly identified, seminal vesicle ectasia do not result in male infertility</td>
<td>No systematic screening</td>
</tr>
<tr>
<td>Thyroid cysts</td>
<td>Case reports</td>
<td>Very limited number of cases. Uncertainty about specific link with ADPKD</td>
<td>No systematic screening</td>
</tr>
</tbody>
</table>

*Table 14. Extrarenal manifestations.* Estimates taken from a single study and should be taken with caution. ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; ICA, intracranial aneurysm; IPMN, intraductal papillary mucinous neoplasms; MVP, Mitral valve prolapse; MVR, mitral valve regurgitation.
Research recommendations

- Studies are needed to better evaluate the frequency of ICA and SAH in people affected by ADPKD, including according to geographic ancestry.
- Research is needed to provide a better definition of the interval between screening for unruptured ICA in the case of a negative screening result.
- Studies are needed to identify the risk factors for ICA rupture. Validation of predictive tools such as the PHASE score in the ADPKD population, or development of specific prognostic tools to predict the risk for rupture in people with ADPKD and unruptured ICA.
- Studies are needed to determine if people with ADPKD and more severe kidney involvement (i.e., Mayo Class 1D–1E) are at increased risk of ICA and SAH.
- Studies are needed to estimate the absolute risks of ICA or SAH according to age, number of affected relatives, smoking status, uncontrolled hypertension, to further discriminate low-risk from high-risk people with ADPKD.
- Studies are needed to identify the genetic factors (e.g., genetic variants coinherited with PKD1 or PKD2 pathogenic variant, polygenic risk scores) responsible for the increased risk of ICA in people with ADPKD.
- Studies are needed to identify the genetic factors responsible for the development of other vascular phenotypes (thoracic aortic dissections, dissections of the cervical and/or the coronary arteries) in ADPKD.
- Studies are needed to clarify whether people with ADPKD have an increased risk of developing abdominal aortic aneurysms.
- Studies are needed to elucidate the potentially protective or harmful effect of pharmacologic agents on the development and rupture of aneurysms (intracranial or aortic) in people with ADPKD.
CHAPTER 7. LIFESTYLE AND PSYCHOSOCIAL ASPECTS

The care of adults with ADPKD is multifaceted and complex. In addition to the direct management of the disease, physicians need to provide patients with advice and guidance regarding nutrition, lifestyle, physical activity, and management of psychosocial issues (Figure 39). Care can be provided by the core multidisciplinary care team or by referral to dedicated services.

Figure 39. Lifestyle and psychosocial care for improved outcomes in people with autosomal dominant polycystic kidney disease (ADPKD). BMI, body mass index; F, female; M, male

7.1. Nutrition intake

ADPKD is a lifelong condition, associated with complications (e.g., hypertension, CVD, kidney failure, kidney stones) that can clearly be affected by dietary measures (Chapter 2 and Chapter 3). There are no large dietary intervention trials in people with ADPKD that would suggest that people with ADPKD should be treated differently than other people with CKD. In the absence of large dietary trials to prevent progression of ADPKD, it is important to maintain good general physical health and to prevent premature CVD. A healthy diet and lifestyle regimen needs to be established early and maintained long-term, with the support of accredited/registered dietitians. Individualized counseling, shared decision-making, and multidisciplinary care are necessary for all people with ADPKD.
**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.**

People with ADPKD should consume a well-balanced diet high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts, and low in processed meats, refined carbohydrates, and sweetened beverages. Adherence to healthy eating practices has been shown to offer numerous health benefits in the general population and in people with CKD G1–G4, and hence its applicability to people with ADPKD is reasonable (Figure 40).544-548

<table>
<thead>
<tr>
<th>Recommended daily intake</th>
<th>Comments and impact on ADPKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water</strong></td>
<td></td>
</tr>
<tr>
<td>≥2 l/day</td>
<td>High water intake prevents kidney stones and may reduce kidney function loss. May need to adjust daily intake depending on concomitant medications, capacity for voiding, and to minimize the risk of hyponatraemia.</td>
</tr>
<tr>
<td><strong>Salt</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium &lt;2 g/day (equivalent to &lt;90 mmol sodium/day or &lt;5 g salt/day)</td>
<td>Recommended by WHO for the general population.6 High salt intake in the observational CRISP (Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease) study and in post hoc analyses of clinical trials in patients with ADPKD has been associated with faster increase in kidney volume and, at later stages (eGFR 25–60 ml/min/1.73 m²), with faster decline in kidney function.” 7-9 Patients should be counselled not to add salt to their food, and to avoid processed foods (typically high in sodium) as much as possible.</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td></td>
</tr>
<tr>
<td>0.8–1 g/kg (weight)/day</td>
<td>Recommended by WHO for general population.93 Increase plant-based protein, compared to animal sources. Benefit of protein restriction has not been demonstrated; however, excess dietary protein (≥1.3 g/kg/day) may be harmful.</td>
</tr>
<tr>
<td><strong>Calories</strong></td>
<td></td>
</tr>
<tr>
<td>25–35 kcal/kg/day, individualized to treat or prevent overweight and obesity</td>
<td>High BMI and obesity are associated with many adverse health conditions and may be associated with accelerated ADPKD progression.10-14</td>
</tr>
<tr>
<td><strong>Fat</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;30% of daily energy intake Saturated fat limited to &lt;10% of total fat</td>
<td>Recommended for general population15-18</td>
</tr>
<tr>
<td><strong>Fiber</strong></td>
<td></td>
</tr>
<tr>
<td>25–38 g/day (14 g per 1000 calories)</td>
<td>Recommended for general population19</td>
</tr>
<tr>
<td><strong>Caffeine</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;400 mg/day</td>
<td>Recommendation by WHO for general population20,21</td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
</tr>
<tr>
<td>A well-balanced diet:1 • high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts • low in processed meats, refined carbohydrates, and sweetened beverages.</td>
<td>Recommended by WHO for general population8 At least 400 g (5 portions per day) of fruit and vegetables, excluding high-starch foods such as potatoes. More specific information on recommended food amounts can be found in the Dietary Guidelines for Americans 2020–202525</td>
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</table>

**Figure 40. Nutrition guideline for people with autosomal dominant polycystic kidney disease (ADPKD) and chronic kidney disease (CKD) G1–G4.**545-548 BMI, body mass index; TKV, total kidney volume; WHO, World Health Organization

**Practice Point 7.1.2: Physicians should work with accredited nutrition providers or registered dietitians to provide individualized nutrition counseling to people with ADPKD, particularly with CKD G4–G5.**

People with ADPKD and CKD G4–G5 should continue healthy-eating practices but may need individualized dietary counseling to prevent the classical metabolic complications of...
advanced CKD including hyperkalemia, metabolic acidosis, and bone and mineral abnormalities. There are currently no studies to suggest that people with ADPKD and CKD G4–G5 should be treated differently from people with CKD from other etiologies. Prevention and treatment of hyperkalemia, metabolic acidosis, and mineral abnormalities are discussed in the forthcoming KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Hyponatremia may develop if people with ADPKD continue high water intake at CKD G4–G5, particularly if they are also treated with other medications that predispose to hyponatremia (e.g., selective serotonin reuptake inhibitor [SSRI]). Water intake needs to be individualized in these people.

**Practice Point 7.1.3:** People with ADPKD should maintain a healthy body weight.

A healthy BMI of 20–25 kg/m² (after excluding the excess weight of severely enlarged kidneys and/or liver, see Practice Point 7.1.5 and Figure 21 in Chapter 3) is important for optimal cardiovascular health. High BMI and obesity are key factors in the development and exacerbation of hypertension, diabetes, hyperlipidemia, and CVD. Because CVD is the most common cause of morbidity and mortality in people with ADPKD, people should be advised to improve all modifiable risk factors to reduce their high risk of cardiovascular problems.

Physicians should also inform patients that obesity itself can cause kidney disease, notably the glomerular disease focal segmental glomerulosclerosis (FSGS), which may be superimposed on ADPKD, thus dramatically accelerating progression due to significant proteinuria. High BMI, with or without associated unhealthy metabolic profiles, is associated with greater risk for kidney failure in people with underlying kidney disease. Furthermore, post hoc analyses of The HALT-PKD and the TEMPO trials also suggest that overweight and obesity are associated with more rapid progression of ADPKD.

The impact of high energy intake and high BMI may be particularly harmful for people with ADPKD because cystic cells are characterized by metabolic reprogramming favoring aerobic glycolysis, making them glucose-avid and dependent on an ample supply of glucose to proliferate. In animal models of ADPKD, caloric restriction significantly decreased the cystic kidney phenotype.

**Practice Point 7.1.4:** Physicians should work with accredited nutrition providers or registered dietitians to help people with ADPKD who are overweight (BMI 25–29.9 kg/m²) or obese (BMI >30 kg/m²) to lose weight.

Weight loss is particularly important for overweight young people with ADPKD who are more able to exercise and who accumulate adverse metabolic features for a long time. As an additional benefit, in the HALT-PKD trial, weight loss of at least 4% per year was also
associated with favorable effects on pain in people with ADPKD.\textsuperscript{566} Daily caloric restriction (rather than intermittent fasting) appears to be the best way to achieve weight loss as indicated in an interventional pilot study.\textsuperscript{567} There is currently no evidence to recommend any specific weight loss diet over others. We particularly advise against a high-protein diet (≥1.3 g/kg (weight)/day). There is currently no evidence to recommend any specific type of diet to lose weight in ADPKD.

Some people may be more motivated to lose weight when they are told that this is necessary for receiving a kidney transplant. However, attempting weight loss at later CKD severities (CKD G4–G5) is controversial and perceived as not always safe because of an increased risk of hyperkalemia, metabolic acidosis and malnutrition.\textsuperscript{568, 569} Dietary interventions often fail to achieve significant weight loss in these people, whereas bariatric surgery has been successful in selected kidney transplant candidates.\textsuperscript{570} Suggestions for multidisciplinary care, including pharmacologic treatment, of people with CKD and obesity are provided in a recent report from the National Kidney Foundation.\textsuperscript{569}

**Practice Point 7.1.5: When calculating BMI, clinicians should take into account the weight of enlarged kidneys and liver.**

Excess weight of enlarged cystic kidneys and liver can be estimated by their volume minus normal kidney and liver weights.\textsuperscript{119} Excess weights should be subtracted from the total body weight to calculate the BMI (Figure 21 in Chapter 3). Note that the normal kidney and liver weights vary to some degree by age, sex, ethnicity, and individual factors.\textsuperscript{571, 572}

**Practice Point 7.1.6: People with ADPKD with poor oral intake due to organomegaly or advanced CKD (G4-G5) should be evaluated for malnutrition or sarcopenia.**

In addition to abnormal kidney function, organomegaly due to massive cysts in the liver and/or kidneys is a risk factor for malnutrition in people with ADPKD (for evaluation of sarcopenia and malnutrition see Chapter 5 Practice Points 5.3.2.2 and 5.3.2.3). Regular assessment of nutritional status and timely intervention by accredited nutrition providers are particularly important for these people.\textsuperscript{573, 38}

**Research recommendations**

- Epidemiological studies are needed to assess the impact of overweight (defined by BMI >25 kg/m\textsuperscript{2}, the presence of the metabolic syndrome or the presence of visceral adiposity), dietary components (e.g., excess carbohydrate, fat, or excess caloric intake) and of specific dietary interventions (e.g., weight loss, low carbohydrate, or low fat intake, or both) on clinical and metabolic features and disease progression in people with ADPKD – taking into account regional specificities.
- Dietary interventions, such as ketogenic diets, and caloric restriction, which have shown
efficacy in animal models of PKD, should be tested in people with ADPKD, using appropriate endpoints and adequately powered clinical trials.

7.2. Physical activity
Maintaining general health and physical fitness is particularly important in a lifelong disease like ADPKD. Physical activity may help to control hypertension and improve cardiovascular health in people with ADPKD. Physical activity contributes to good QoL, counteracts depression and maintains a healthy body weight. Physical fitness is essential for people with kidney failure, so that they are good candidates for kidney transplantation. Despite a small risk of cyst hemorrhage (see below), cystic kidneys and/or liver are not a contraindication to 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 at least 2 days per week.

The health benefits of regular physical activity are well-known. Even though there are no specific studies examining the impact of physical activity in ADPKD, the Work Group agrees that Practice Points 3.2.1–3.2.3 from the KDIGO Clinical Practice Guideline for the Management of Diabetes in CKD can also be applied to people with ADPKD. Briefly, clinical advice for physical activity should consider age, ethnic background, presence of other comorbidities, access to resources and risk of falls (among people with sarcopenia). People with ADPKD should be advised to avoid sedentary behavior and should be encouraged to undertake regular activities to improve or maintain muscle strength, balance, and flexibility, and should break up prolonged periods of being sedentary with light activity.

Most people with ADPKD can follow guidelines that recommend that adults (≥18 years) perform at least 150 minutes per week of moderate-intensity exercise. Those who are already regularly active can achieve these benefits through 75 minutes of vigorous intensity activity per week, or a combination of moderate and vigorous activity (Figure 41).

Because physical inactivity is a modifiable risk factor, physicians should routinely assess the level of physical activity and, if necessary, prescribe structured exercise and increased lifestyle activities to all people with ADPKD.
Practice Point 7.2.2: People with large kidneys and/or liver should be advised of the possibility of direct injury during physical activity and exercise.

Direct injury can cause hemorrhage and/or rupture of kidney and/or liver cysts which causes sudden onset, localized sharp pain. Approximately 50% of people with ADPKD and ruptured kidney cysts have macroscopic hematuria due to the ruptured cyst communicating with the collecting system.576

Direct trauma to kidneys and/or liver is a particular concern for contact sports, and bleeding is more likely to occur if cysts are superficially located and large. Therefore, people with ADPKD and large and/or superficial cysts should be advised to avoid collision or contact sports (e.g., American football, rugby, boxing, hockey, lacrosse, wrestling, judo, etc.) and to use protective equipment such as an athletic “corset”.

If a particular type of physical activity is consistently associated with macroscopic hematuria and/or flank pain (presumed cyst ruptures) in a person, it is best to avoid this activity. This suggestion is based on the belief that bleeding due to cyst ruptures leads to subclinical kidney injury and, thereby, accelerates the progression of ADPKD.

On the other hand, hematuria may occur in absence of direct trauma, such as after running and jumping, presumably because of stretching or abruptly changing forces on small blood vessels in cyst walls. Since hematuria episodes can also occur at rest and most people with ADPKD exercise without resulting hematuria, in the judgement of Work Group, given the large
health benefits of regular physical activity, it is not appropriate to discourage exercise for people with ADPKD, particularly for young people.

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

There are many barriers to exercise for high-risk people. The most important barriers are fatigue and weakness due to comorbidities or to the dialysis procedures, lack of time and equipment, lack of a place to exercise, and cost of going to a gym. People with ADPKD being treated with dialysis and transplantation should undertake as much physical activity as they are able to. People receiving dialysis frequently have reduced aerobic and functional capacity, high risk of cardiovascular disorders, and muscle atrophy. A sedentary lifestyle characterizes them and contributes to the aggravation of the disorders. On the contrary, exercise training is an important preventive and therapeutic tool both for cardiovascular problems and for the appearance of muscle atrophy in people receiving dialysis.\(^{577}\)

**Research recommendations**
- Epidemiological studies are needed to assess the risks and benefits of specific forms of exercise in people with ADPKD, using appropriate outcomes and powered cohorts.
- Studies are needed to assess whether protective equipment such as an athletic “corset” decrease episodes of cyst hemorrhage.

**7.3. Lifestyle management**

The optimal medical care of people with ADPKD may be best provided by a team of healthcare providers who practice at a single site, following the principles of the chronic disease model of care and specialized clinics for genetic diseases (Chapter 10).\(^{578}\)

**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.

Smoking and other use of tobacco products increase the risk of subclinical and overt atherosclerosis. People with ADPKD who use tobacco products have more cardiovascular and cerebrovascular events than nonsmokers, higher risk of intracranial and other aneurysmal formation and rupture, likely accelerated progression of ADPKD, more endothelial dysfunction, and more proteinuria than nonsmokers.\(^{158, 462, 470, 579, 580}\) People should be asked about their use of
tobacco products intermittently, since they may change their use (e.g., starting or stopping smoking) at any time during their lives.

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 for women or ≤2 drinks per day for men.

People with ADPKD who consume alcohol should follow guidelines for alcohol consumption in the general population. Light alcohol consumption may decrease cardiovascular risk. Moderate alcohol consumption does not appear to be substantially associated with higher or lower risk of abnormal kidney function. However, alcohol intake above recommended levels is clearly associated with increased mortality and other medical morbidities, including cancer. An important consideration for people is that the WHO recognizes that alcohol is a toxic and psychoactive substance with dependence-producing properties that has the potential to reduce the QoL for people and their loved ones.

While there are no studies to suggest that people with ADPKD should stop or reduce drinking alcohol, a systematic review found that excessive alcohol intake (>150 g per week) was a significant risk factor for subarachnoid hemorrhage in both the longitudinal (relative risk [RR]: 2.1; 95% CI: 1.5–2.8) and case-control studies (OR: 1.5; 95% CI: 1.3–1.8). This association was confirmed in a subsequent meta-analysis which also found evidence of a linear dose-response.

Physicians should advise people with excessive alcohol consumption, particularly young people, to reduce or stop drinking in collaboration with alcohol use disorder clinic or its equivalent for behavioral and pharmacologic intervention. Physicians should counsel people to drink additional water when they consume alcohol to avoid harmful dehydration.

People should be asked about their use of alcohol intermittently, since they may change their use (e.g., starting, stopping, or increasing intake) at any time during their lives.

7.3.3. Cannabis products

Practice Point 7.3.3.1: All people with ADPKD should be asked about their use of cannabis products and should be counselled about potential dangers of acute kidney injury (AKI) related to product contamination and synthetic versions.

People with ADPKD are at greater risk for AKI due to decreased kidney function. There are case reports on synthetic cannabinoids causing significant AKI. Currently, there is no evidence of clinical benefits of cannabis beyond anecdotal case reports. It is important to note that the toxicity of these products is not always due to the drug itself but to its contaminants which are
often unknown to the user. In absence of dedicated studies, the use of medical cannabis products to alleviate complications in people with ADPKD is not advised.

People should be asked about their use of cannabis products intermittently, since they may change their use (e.g., starting, stopping, or increasing intake) at any time during their lives.

7.3.4. Nephrotoxins
Practice Point 7.3.4.1: All people with ADPKD should be asked about their use of recreational drugs and anabolic steroids and should refrain from these drugs.

Cocaine and methamphetamines can cause elevated BP, hypertensive crises, and vasoconstriction which could potentially increase the risk of ICA rupture. There are numerous case reports of cocaine and other drugs of abuse leading to AKI requiring dialysis that may not always resolve.\textsuperscript{586, 587} Illicit drug use and chronic misuse of anabolic steroids is also strongly associated with increased risks of CKD and kidney failure.\textsuperscript{588-593}

People should be asked about their use of recreational drugs and anabolic steroids, since they may change their use (e.g., starting, stopping) at any time during their lives.

Research recommendations

- Studies are needed to assess the risks versus benefits of using medicinal cannabis products for relief of chronic pain and other symptoms in ADPKD.
- Epidemiological studies are needed to analyze the association of specific nephrotoxins with the outcome of ADPKD.

7.4 Psychosocial care
Practice Point 7.4.1: Healthcare providers should monitor a patient’s psychological health and social needs during clinic visits (Figure 42). Healthcare providers should screen and conduct periodic assessment of psychosocial issues in people with ADPKD (Figure 43).

People with ADPKD and their families are subject to a range of psychosocial stressors following diagnosis and during their life, both before and after development of kidney failure (Figure 43). Some may need psychological interventions and/or referral to social care services.\textsuperscript{594, 595}
Figure 42. Stressors associated with psychosocial problems in people with autosomal dominant polycystic kidney disease (ADPKD).

Figure 43. Psychosocial manifestations, screening, and management. *See Appendix A

Anxiety and depression

Anxiety and depression are highly prevalent in people with CKD and are reported by >60% of those with ADPKD. Female sex, increased kidney size, progression to kidney failure, and loss of a first degree relative with ADPKD were identified as independent risk factors for increased psychosocial risk. Anxiety over an uncertain future should be anticipated in young people before and after pre-symptomatic testing/diagnosis.

Physicians may underestimate and overlook psychological issues in people with ADPKD, especially in the early stages. However, physicians caring for these patients need to understand
that many people are having thoughts such as: How long will I live?, Is it worth it to pursue an ambitious career if I'm going to die young?, Will I be able to have children, or live long enough to raise them?, Will anyone want to marry me with ADPKD? Psychological problems in people with ADPKD can manifest as nonspecific, somatic symptoms, such as pain, depression, lack of energy, etc. Symptoms such as abdominal distension, sleep disturbances, and pain impair overall QoL in people with ADPKD.

If ignored, psychosocial issues can lead to a socioeconomic burden for people which stems from career and financial planning decisions that could negatively impact people and their families for years to come. Therefore, healthcare team should be aware of the psychological support needs of people with ADPKD in different stages of life.

There are no guidelines specifying the timing and/or interval of psychological screening in people with ADPKD. However, given the prevalence and diverse manifestations, it would be prudent to review them annually. The use of standardized preclinic visit planning tools for screening and identification of psychosocial issues in people with ADPKD should be considered (Appendix A).

**Body image and sexual dysfunction**

As ADPKD progresses, many changes happen to a person that can have negative impacts on body image and sexual function. Concerns about body image are linked to anxiety and depression. Some people with enlarged or deformed abdomen linked to cystic kidneys or liver, for instance, experience negative body image issues that can affect sexual function. Many people have reported feelings of being “defective” or “ugly,” including fears of being rejected by their partner.

Normal sexual function for males and females includes interactions among vascular, neurologic, hormonal, and psychological systems. Common sexual dysfunction risk factors that apply to people with ADPKD include CVD, medications, and psychosocial aspects. Multiple studies have shown how a negative body image can lead to sexual dysfunction. The sexual dysfunction itself, which could be caused by medication or other ADPKD effects, can lead to mental health issues, including depression. Sexual and reproductive function abnormalities are frequently observed in people with CKD G4–G5.

**Genetic guilt**

The hereditary nature of ADPKD, the risk of disease transmission to the next generation, and the risk of the condition among a person’s extended family can pose major psychological challenges. The burden of “genetic guilt” among people with ADPKD but also nonaffected members of the family is a unique feature in inherited diseases including ADPKD.
Appropriate education about genetic diseases (“genetic literacy”) and counseling should be provided to people with ADPKD and family members (Chapter 1).

**Chronic pain**

Chronic pain is a common cause of psychosocial issues in people with ADPKD. Studies have shown that 60% of people with ADPKD are impacted by chronic pain. Physicians should include a psychosocial approach for management of chronic pain of intense and repeated nature that has not responded to initial medical and/or surgical treatment. The appropriate initial therapeutic strategy for chronic pain of psychological origin depends upon an accurate evaluation of the cause of the pain and the type of chronic pain syndrome. Pain is dealt with in detail in Chapter 2; however, physicians should still discuss with people how chronic pain may be affecting their lives.

**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.**

Comprehensive and practical information about ADPKD that is easy to understand should be provided to people with ADPKD and their families by a professional healthcare team to promote their own self-care. Key objectives of self-management education are to:

- improve ADPKD-related knowledge,
- improve self-management and self-motivation,
- encourage adoption and maintenance of a healthy lifestyle,
- improve emotional and mental well-being, treatment satisfaction, and QoL.

Learning needs should also be monitored regularly. Figure 44 summarizes information for people with ADPKD and caregivers.

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.

ADPKD-focused patient organizations, national kidney federations, and kidney patient support groups can help people and families with ADPKD through the provision of information, sources of financial support and assistance, and peer support. These organizations and groups exist in many countries. For a list of those supporting people with ADPKD and families, see www.pkdinternational.org.

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

Physicians may underestimate the financial burden to people with ADPKD, and if not discussed, people may feel isolated, resulting in missed appointments, reluctance to testing or treatments, and poor rapport with those involved in their care. Therefore, healthcare teams must be aware of the social and financial situation of people with ADPKD; costs of expensive medications (e.g., tolvaptan) relative to their expected benefits need to be discussed. Healthcare teams should provide country-specific information on sources for financial support for medications, kidney replacement therapies and caregiver needs, as well as on legal protection against discrimination regarding employment, mortgages, and life and health insurance.
Research recommendations

- Studies are needed to validate and, ideally, compare, existing tools for assessing patient-reported outcomes in people with ADPKD.
- An incidence-based approach for examining anxiety and depression linked to ADPKD in general, analyzing differences in geographic, cultural, and other demographic factors.
- Studies are needed to assess the effects of body dysmorphia on mental health and sexual dysfunction on people with ADPKD.
- Studies are needed to assess various interventions for mental health, and psychological aspects of chronic pain and sexual dysfunction in people with ADPKD.
- Studies are needed to assess the optimal psychological support (e.g., counseling, intervention, etc.) for people with ADPKD and their families, considering age at diagnosis.
- Online tools should be created to assist people with CKD with getting help for body image and sexual dysfunction issues, considering cultural and regional specificities.
- Socioeconomic studies assessing the financial and societal burden of ADPKD are needed to inform policy and coverage decisions. These should be conducted to assess the variation in coverage and healthcare systems throughout the world.
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, preconception counseling, and pregnancy management (Figure 45).

Figure 45. Management of women with autosomal dominant polycystic kidney disease (ADPKD) of childbearing age. BP, blood pressure; CKD, chronic kidney disease; HRT, hormone replacement therapy; HTN, hypertension; IUD, intrauterine device; OCP, oral contraceptive; PGT, preimplantation genetic test; PLD, polycystic liver disease (>10 cysts in the liver); PT, prenatal test; RASi, renin-angiotensin inhibitors; UTI, urinary tract infection

Practice Point 8.1.2: Since estrogen and possibly progesterone exposure may associate with an increased risk of PLD progression, women with ADPKD and liver cysts should be educated regarding their contraceptive choices (Chapter 5).

Practice Point 8.1.3: Contraception in adolescents should not be restricted.

Contraception is achieved using hormonal (estrogen-based, progestin-based, or combined hormonal contraception) or nonhormonal methods. It is generally accepted that estrogens promote the progression of PLD. The disease is more severe in women than in men, liver volume increases in premenopausal females but stabilizes in post-menopause, and estrogen replacement after menopause is associated with an increase in liver volume compared to post-menopausal with ADPKD women not taking estrogens.\textsuperscript{385, 407, 409} Although data are limited, it suggests that exposure to estrogen-containing contraceptive is associated with more PLD and greater liver volume in ADPKD women.\textsuperscript{408} Preclinical evidence demonstrate that estrogens stimulate proliferation of intrahepatic biliary epithelium in rats.\textsuperscript{612} The severity of PLD varies widely among people with ADPKD and liver involvement can be minimal or very mild in women with
many pregnancies or years of exposure to estrogen-containing contraceptives. Therefore, estrogen-based and combined hormonal contraception can be used under supervision in people with mild PLD but should be avoided in people with moderately severe or severe PLD (Chapter 5).

Combined hormonal (estrogen and progestin) contraceptives can be used in people with ADPKD with or without mild PLD. Available combined hormonal contraceptives include oral contraceptive pills, transdermal patches, and intravaginal rings. Combined oral contraceptives containing low estrogens (10 to 35 µg ethinyl estradiol) are generally preferred. Patches and intravaginal rings avoid the first-pass liver effect and may have less impact on PLD. An advantage of the patches is the steadiness of estrogen levels without the peaks and troughs seen with oral contraceptives, however, the estrogen AUC is higher. Intravaginal rings allow for lower serum estrogen concentrations than those with pills or patches.

Progestin-only methods include pills, injections, implants, and IUDs. The systemic exposure to levonorgestrel with levonorgestrel-releasing IUDs is 4%–13% of circulating levels found with oral combined hormonal contraceptives. Rat cholangiocytes express progesterone receptors and are stimulated by progesterone and inhibited by antiprogestereon antibodies. Progestin-only contraceptives could also stimulate the growth of cysts in livers of people with ADPKD. However, progestin-only contraceptives and estrogen-containing contraceptives have been shown to respectively inhibit and stimulate the growth of hepatocellular adenomas despite the expression of both progesterone and estrogen receptors in these lesions. The impact of progestin-only contraceptives on liver volume in people with ADPKD is not known and is an important topic for future research.

Nonhormonal contraception methods which are completely free of exogenous estrogens include barrier-based forms of contraception (condoms, diaphragm, cervical caps, contraceptive sponges, and vaginal spermicides) and copper IUDs and possibly progestin-only IUDs. These are the safest anticonception methods for people with severe PLD.

When considering contraceptive options in women with ADPKD, the probability of contraception failure should be considered. Failure rates for the above-mentioned contraception options are highest for barrier-based options and lowest for IUDs.

Informed discussion should be offered for the use of hormones for dysmenorrhea, menopausal symptoms, or postmenopausal maintenance of bone density in women with evidence of PLD. Alternatives to estrogens or progesterone should be encouraged in those people with ADPKD and severe PLD.
Practice Point 8.1.4: When considering hormone therapy in women with ADPKD, liver imaging should be made available to inform discussion about options for contraception, hormonal replacement, and other indications (Chapter 5).

Decisions on the use of hormone therapy should consider the presence and severity of PLD; however, no staging system for disease severity has been established so far. Although it is advised to minimize the use of oral contraceptives containing estrogens and possibly progestins in people with PLD, when they are prescribed, it seems wise to monitor their effect on PLD by intermittent liver imaging, including volumetry when feasible.

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.

Practice Point 8.2.2: Preconception counseling should be provided by a multidisciplinary team in an ADPKD referral center when possible (Figure 46).

Figure 46. Multidisciplinary approach to preconception counseling. *Other specialties may be involved depending on the case (e.g., hepatologist, neurologist, etc.)

Preconception counseling encompasses everything from drug adjustment in women with ADPKD, reproductive options, potential pregnancy outcomes, and anticipated risks for the mother and the child at risk of inheriting ADPKD. Preconception counseling should be carried out by qualified providers. Primary care providers, nephrologists, and/or genetic counselors can be involved (Figure 46). The attitude towards different reproductive options in ADPKD will vary based on individual values, medical availability and potential intrafamilial variability of disease severity.
Practice Point 8.2.3: People with ADPKD at reproductive age should be offered appropriate counseling and all available reproductive options (Figure 47).

**Figure 47. Reproductive options for people with ADPKD.** ADPKD, autosomal dominant polycystic kidney disease

**Prenatal testing of the fetus.** The purpose of prenatal testing is to determine whether the fetus has ADPKD. This option should be offered only to parents who would consider pregnancy termination/abortion (with discussion about the availability of legal abortion). Invasive genetic testing is available during pregnancy at weeks 10–12 of gestation using chorionic villus sampling. The procedure involves a risk of total pregnancy loss and spontaneous miscarriage of approximately 1%. Prenatal cell-free DNA screening which is available from week 10 of gestation involves detection of fetal cells in maternal blood, but there is no evidence of how well this test performs in detecting ADPKD mutated cells from the fetus.

**Preimplantation genetic testing (PGT).** PGT entails genetic testing of 1 to 4 cells derived from an early-stage embryo after IVF with intracytoplasmic sperm injection. To avoid transmission of ADPKD to the fetus, only embryos without the parental mutation in the biopsied cell(s) are eligible for transfer into the uterus. The main advantage of PGT is that it avoids abortion and confirms that the child will be unaffected. However, this option should be offered only to families with a confirmed causal pathogenic variant who prefer disposal of unimplanted embryos affected by ADPKD. The procedure should follow the European Society of Human
Reproduction and Embryology (ESHRE) PGT Consortium good practice recommendations.619, 620

Ovarian stimulation for IVF requires high doses of hormones that may increase cyst growth in PLD and increases the risk of AKI and ovarian hyperstimulation syndrome. Women with ADPKD must be advised regarding the risks in the setting of ovarian stimulation. In women with severe PLD and advanced abnormal kidney function, IVF should be discouraged due to these concerns. No increased risk of complications has been reported in pregnancy from PGT in ADPKD; however, there are limited data to evaluate this. The chances of a successful pregnancy using PGT is approximately 30%–40%. The live birth delivery rate significantly declines with female age in ADPKD, like the general population.621

The uptake of PGT for ADPKD is growing worldwide,622 although some religious organizations disapprove of this procedure. It is also not widely available throughout the world. In some countries and jurisdictions, it is covered by the public health system or insurance, while in others, it is extremely expensive, or the waiting list is very long.

*Artificial insemination by sperm donation.* Artificial insemination with donor sperm involves controlled or stimulated ovulation with placement of unaffected donor sperm inside the uterus on the day of ovulation. This is a reproductive option to consider when the male partner has ADPKD. In the case where the unaffected male partner is infertile, sperm donation would entail less risk of worsening PLD in the affected female as hormonal therapy doses are much lower than in PGT. Prospective parents should be advised that the sperm donor will be the biological father of the baby. Sperm banks typically screen potential donors for specific genetic diseases, chromosomal abnormalities, and sexually transmitted infections that may be transmitted through sperm.

*Egg donation.* Egg donation is the process by which a woman donates her eggs to enable another woman to conceive as part of an assisted reproduction treatment. Egg donation typically involves IVF technology. This approach could be used when the female partner has ADPKD. However, given the fact that this procedure involves IVF, there is uncertain uptake for this option in ADPKD when PGT is available. It could be useful in cases of women with severe PLD where IVF is discouraged or when a causative mutation cannot be identified. Couples should be advised that in cases where the pregnancy goes to full term, the egg donor will be the biological mother of the baby.

If these reproductive options prove not to be viable, adoption is always an option.
Practice Point 8.2.4: Tolvaptan, RASi (i.e., ACEi and ARBs), and any other teratogenic drug should be stopped prior to pregnancy and not restarted until the mother has completed breastfeeding.

There are minimal observational data in human pregnancy to determine if there is a drug-associated risk of adverse developmental outcomes with tolvaptan; therefore, it is considered a Class D drug in pregnancy. In animal studies, tolvaptan was shown to cause cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryofetal death. Tolvaptan may easily be transferred to breast milk; therefore, the use of tolvaptan during breastfeeding is contraindicated. Women of childbearing age should use adequate contraceptive measures during treatment with this drug. Tolvaptan should be discontinued in women who are planning a pregnancy.

Drugs that inhibit the RASi, including ACEi and ARBs, are considered class D drugs in pregnancy and are not advised because of their potential fetal toxicity. The best approach is to stop these medications in women who are planning pregnancy, and if necessary, change to more appropriate antihypertensives for pregnancy (i.e., labetalol, nifedipine long-release, hydralazine, clonidine, or methyldopa). RASi are potentially teratogenic in the first trimester of pregnancy. They can cause reduced fetal kidney function, oligohydramnios, and skull hypoplasia in the second and third trimesters of pregnancy. Women who have become pregnant while taking ACEi or ARBs should be made aware of the exposure risk versus the safety of temporary use in pregnancy.615 These agents need to be stopped and if necessary switched to other antihypertensive medications for the duration of their pregnancy. During breastfeeding, ACEi, including enalapril or captopril, can be safely reintroduced if other agents are not adequately controlling blood pressure.623

Practice Point 8.2.5: Although men with ADPKD demonstrate increased prevalence of seminal tract cysts and sperm abnormalities, these do not appear to impact fertility, therefore, systematic screening is not indicated.

Studies have demonstrated a higher prevalence of seminal tract cysts and sperm abnormalities (necrospermia, ultrastructural flagellar defects, and immotile sperm) in men with ADPKD, rarely associated with male infertility.624, 625 Whether the frequency of male infertility in ADPKD is higher than in the general population is not known, but it does not appear to be high enough to warrant a systematic preconception evaluation.

Practice Point 8.2.6: Before pregnancy, screening for ICA should be considered in women with family history of ICA.
There is no evidence of increased risk for ICA rupture during pregnancy or vaginal delivery. Systematic screening for ICA before pregnancy or delivery in women with ADPKD is not usually performed. Nevertheless, screening for ICA is advised in people with a family history of ICA or SAH, particularly in a first degree relative (Chapter 6). If an ICA is found, decisions regarding need, timing and type of intervention should be made by specialized neurosurgeons or interventional radiologists. There is no available evidence to alter the BP goal with known ICA.

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.

A pregnant woman with ADPKD should be monitored by an obstetrician and a nephrologist. However, in certain circumstances, other specialists such as hepatologists and neurologists may be needed (Figure 46). Given the potential risks of pregnancy and the need for a multidisciplinary team, it is advisable for the pregnancy to be followed either fully or in collaboration with a medical center with expertise in ADPKD and pregnancy, or CKD and pregnancy.

Practice Point 8.3.2: During pregnancy, BP, kidney function, and proteinuria should be monitored in women with ADPKD, similar to women with CKD.

There is no specific evidence for how best to manage BP in people specifically with ADPKD during pregnancy. Although most women of child-bearing age have normal GFR, some may have decreased kidney function. Guidelines are available for the management of pregnancy in CKD from the United Kingdom (UK) Renal Association. These guidelines may be used in the setting of pregnancy in ADPKD.

Kidney function in pregnancy is assessed using SCr concentration since eGFR is not valid for use in pregnancy. Mean values for SCr in pregnancy are 84%, 77%, and 80% of nonpregnant mean values during the first, second, and third trimesters, respectively. Quantification of proteinuria is undertaken by urine protein-to-creatinine ratio or urine albumin-to-creatinine ratio. This should be done regularly (tailored to severity of CKD; if eGFR>90 ml/min per 1.73 m², the usual pregnancy lab test should be ordered) in conjunction with home BP monitoring as opposed to office BP monitoring, if possible. Twenty-four hour urine collection for quantification of proteinuria is not required.

Practice Point 8.3.3: Pregnant women with ADPKD should undergo monthly urinalyses performed. If a patient has a repeatedly positive urine culture, even when asymptomatic, they should be treated with appropriate antibiotics, as in the general population.
A review of the evidence from the US Preventive Services Task Force concluded with moderate certainty that screening for and treatment of asymptomatic bacteriuria in pregnant women has moderate net benefit in reducing perinatal complications and that treatment of screen-detected asymptomatic bacteriuria can reduce the incidence of pyelonephritis in pregnant women.\(^{628}\) It is recommended to validate an initial positive culture with a second positive culture due to the possibility of specimen contamination during collection and the temporary nature of asymptomatic bacteriuria.\(^{629}\)

Women with ADPKD have a 14% greater risk of UTI during pregnancy compared with people without ADPKD.\(^{630}\) The risk is higher in people with greater h\(r\)TKV.\(^{631}\) UTIs increase the risk of spontaneous labor and preterm delivery in the general population.\(^{632}\) Therefore, treatment of UTIs is important and should be done quickly after a positive culture has been obtained. Women with ADPKD and a positive urine culture, in absence of temperature or signs of cyst of renal parenchyma involvement or more severe renal parenchymal infections (i.e., kidney cyst infections [Chapter 2]), should be treated for 5–7 days.

**Practice Point 8.3.4: Women with ADPKD can safely undergo vaginal delivery, similar to the general population.**

There is no evidence indicating that TKV or kidney transplant impacts the type of delivery. Increased age and decreased kidney function prior to pregnancy increase the risk for complications during pregnancy. Uneventful pregnancies do not appear to influence long-term kidney outcomes in women with ADPKD. However, in a large prospective observational study with historical data on 602 pregnancies in women with ADPKD, increased risk for kidney disease progression was seen in those with \(\geq 4\) pregnancies. Importantly in this study, maternal age and eGFR at the time of pregnancy were not accounted for.\(^{633}\)

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

Pregnant women can safely undergo ultrasound or MRI in any trimester and there is no evidence that these procedures cause harm to the baby. While routine obstetric ultrasound is performed regularly during pregnancy, it is typically done to evaluate the fetus and not maternal abdominal organs. In the presence of abdominal pain, an abdominal ultrasound or MRI can be obtained to further evaluate the mother.
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, most importantly, in those with preexisting hypertension or hypertension diagnosed during their pregnancy.

Gestational or pregnancy-induced hypertension is more frequent in women with ADPKD than in unaffected women. There is no direct evidence evaluating HBPM in women with ADPKD specifically, however, general guidelines for women at high risk for pregnancy-induced hypertension, which include all women with ADPKD, recommend HBPM. 630

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

Although not specific to ADPKD, guidelines for chronic hypertension in pregnancy and in women with CKD who are pregnant are available and several suitable medications can be used in hypertensive women with ADPKD during pregnancy. These include oral methyldopa, labetalol, clonidine, oxprenolol, and nifedipine, and second- or third-line agents including hydralazine and prazosin. 635-637 RASi are contraindicated and diuretics should not be used to treat hypertension in pregnancy.

Decisions regarding the initiation of antihypertensive therapy during pregnancy in women with ADPKD should consider the benefits and harms for both the mother and baby. The risks of BP elevation in the mother with the potential impact on progressive abnormal kidney function need to be considered in the context of adequate placental perfusion. Although the HALT-PKD trial shows benefits of rigorous BP control (<110/75 mm Hg) in young people with ADPKD, these are long-term benefits that impact the rate of increase in TKV and decline in eGFR over 5 years in a nonpregnant population. 148 Given the relatively short time interval of pregnancy with the known hemodynamic changes that occur to maximize placental blood flow and perfusion, BP target in pregnant women with ADPKD is similar to that for all people with CKD, ≤135/85 mm Hg. 626

8.5. Preeclampsia

Practice Point 8.5.1: Women with ADPKD are at an increased risk of preeclampsia and preterm delivery and should be carefully monitored throughout their pregnancy and in the postpartum period.

Preeclampsia, classically considered to be the clinical presence of increased BP, proteinuria, and edema is an explosive disorder that leads to poor pregnancy and perinatal
outcomes in general and occurs more frequently in women with ADPKD.\textsuperscript{630,638} It is a multisystem progressive disorder characterized by the new onset or worsening of preexisting hypertension and at least one sign of maternal end-organ dysfunction (elevated liver enzymes, elevated lipase, low platelet counts) with or without proteinuria in the second half of pregnancy or postpartum.\textsuperscript{639,640} It is a placental disorder that results in endothelial dysfunction and may result in seizures (eclampsia) and is associated with increased maternal mortality, preterm delivery, and low birthweight.

Preeclampsia is a known risk factor for future kidney failure in the general population and is also a known cardiovascular risk factor. While the relationship between the development of preeclampsia and the future kidney failure in women with ADPKD has not been studied, in all forms of CKD, preeclampsia has been associated with an increased risk for kidney failure.\textsuperscript{640}

While preeclampsia typically develops in the latter part of the third trimester, early onset preeclampsia has been reported occasionally even before the 20th week of pregnancy in women with preexisting chronic hypertension and/or CKD, with resultant intrauterine growth retardation and severe prematurity. Circulating angiogenic factors (sFlt1 and placental growth factor [PIGF]) contribute to the endothelial dysfunction underlying the pathogenesis of preeclampsia. Their elevation in plasma predates the clinical manifestations and predicts maternal and fetal outcomes.\textsuperscript{641} Unfortunately, the utilization of these tests is limited by their availability.

Figure 48 shows the clinical signs and symptoms of preeclampsia with and without proteinuria. Note that not all signs and symptoms need to be present in women with preeclampsia.
Figure 48. Diagnostic criteria for preeclampsia. 638

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 (Figure 45).

Low-dose aspirin has been shown to reduce the incidence of preeclampsia in high-risk women. There are minimal data on the use of low-dose aspirin in women with ADPKD during pregnancy; however, pregnant women with ADPKD are considered high-risk based on the presence of kidney disease and are considered to be at higher risk for preeclampsia if they have preexisting hypertension or abnormal kidney function. Therefore, consistent with international guidelines for pregnancy, women with ADPKD should take 75–150 mg of aspirin daily, starting at 12 weeks gestation (preferably no later than 16 weeks), until 36 weeks gestation.

The benefit of low-dose aspirin needs to be balanced against potential harm. A retrospective analysis of 663 people with ADPKD in the DIPAK observational cohort showed that use of aspirin (325 mg/day) was associated with a 2-fold higher frequency of macroscopic hematuria in men and nonpregnant women. Nevertheless, the overall risk was low and the episodes of macroscopic hematuria were self-limited. These data suggest that the benefit of aspirin for prevention of preeclampsia outweighs the risk of cyst bleeding, especially at the low suggested doses.
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 outcome. 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 higher risk of poor neonatal outcome or early onset childhood kidney dysfunction.

Features occasionally seen on prenatal ultrasound, including enlarged echogenic kidneys, abnormal corticomedullary differentiation, and/or kidney cysts, are not specific to ADPKD. While MRI can often better delineate structural kidney anomalies, it is not sufficient to differentiate fetal ADPKD from other cystic kidney diseases. In the setting of a known parental history of ADPKD, however, such sonographic findings will likely lead to a diagnosis of ADPKD in the fetus.

The mere detection of prenatal findings suggestive of ADPKD does not necessarily reflect postnatal disease severity, as with serial monitoring, such children may show normalization of kidney size and limited progression in early childhood. If definitive diagnosis is required, genetic testing is confirmatory. Importantly, however, extensive fetal cystic kidney involvement or evidence of abnormal kidney function in the fetus (e.g., oligoanhydramnios) portends poor postnatal and childhood outcomes. Such severe cases may warrant proper genetic testing (Chapter 1). Termination of pregnancy may be considered when significant fetal dysfunction leading to Potter sequence (i.e., atypical physical appearance of a baby due to oligohydramnios experienced when in the uterus. It includes clubbed feet, pulmonary hypoplasia and cranial anomalies related to the oligohydramnios) is present. However, this situation suggests ARPKD, not ADPKD.

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.

The sensitivity of ultrasound in the fetus to detect ADPKD is low. Kidney cysts develop and enlarge over time, and the majority of fetuses with ADPKD will not demonstrate kidney cysts of sufficient size to be detected by current ultrasound resolution. Therefore, in an at-risk fetus, it is important to convey to parents that a normal kidney ultrasound in fetal life, or even in childhood, does not exclude the diagnosis of ADPKD (see Chapters 1 and 9).
8.7. Postpartum care

Practice Point 8.7.1: Women with ADPKD should be seen by a nephrologist early (6 weeks) after delivery for a post-partum kidney review (Figure 49).

Estimated GFR typically returns to pre-pregnancy levels towards term or shortly after delivery.\(^{627}\) BP, which typically declines during pregnancy, will increase after delivery and HBPM should preferably be performed. BP control after delivery should target <110/75 mm Hg based on the findings of the HALT-PKD trial (Chapter 2).\(^{148}\) The choice of antihypertensive agent should depend on whether breastfeeding is taking place.

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 when tolvaptan will be prescribed.

Bladder instability and urinary incontinence are quite frequent (approximately 15%) after pregnancy in women.\(^{649, 650}\) Nephromegaly, hepatomegaly, and the habit of drinking large volumes of water, present in many pregnant women with ADPKD, may increase the risk of urinary incontinence. Although pelvic floor physical therapy is advised for bladder instability post-partum in all women, it may have a particular role in women with ADPKD who plan to take tolvaptan considering that the drug will cause polyuria with often nocturia.

Figure 49. Post-partum kidney review.

Research recommendations
- Sufficiently powered epidemiological studies are needed to determine the risk for preeclampsia in ADPKD women. These should be multicenter, cooperative, prospective studies of pregnancies in people with ADPKD to assess maternal outcomes, effects on
kidney and liver cyst burdens, and changes in kidney function, considering various backgrounds and areas.

- The impact of TKV, hTKV, and MIC on the need of special delivery procedures, risk of cyst bleeding, and pregnancy outcomes needs further research. Studies should be multicenter, cooperative, and prospective in nature and should assess the effects of MIC on maternal and fetal outcomes in pregnancies in people with ADPKD.
- Studies are needed to determine the scope and significance of ultrasound findings in fetuses at risk for ADPKD and their correlation with outcomes.
- Studies are needed to examine the magnitude of the effect of estrogens and progesterone on PLD, including ovarian stimulation for IVF and predictors of individual risk.
- Studies are needed to determine the impact of progestin only oral contraceptives on the growth of liver cysts compared to combined hormonal contraceptives and nonhormonal contraceptive methods.
- In consideration of the best choice of combined hormonal contraceptives, studies are needed to better identify young women with mild PLD who may develop severe PLD as they get older.
- Studies are needed to examine the effect of intrauterine levonorgestrel-releasing devices in people with ADPKD.
- Studies are needed on the development and progression of PLD in adolescents and young adults using MRI.
- Studies are needed to define the effects of hormonal replacement on liver cyst growth after menopause.
- Studies examining the impact of ICA screening during or before pregnancy are needed. These should be multicenter, cooperative, prospective study of ADPKD pregnancies assessing the impact of screening, BP control, and type of delivery on ICA rupture.
- Studies are needed to determine the safe target level of BP control for people with ADPKD during pregnancy.
- Studies are needed to determine the use of circulating angiogenic factors (sFlt1 and PIGF) for early detection of preeclampsia in ADPKD. Specifically, this should be a multicenter, cooperative, prospective study assessing the value of circulating angiogenic factors (sFlt1 and PIGF) for early detection of preeclampsia.
- Studies are needed to assess the barriers for access to PGT and the reliability of PKD1 mutation detection in PGTD. This should include a survey of people with ADPKD and physicians evaluating their awareness and attitudes towards PGT, and identification of access barriers.
- A retrospective series assessing outcomes of PGT in people with ADPKD is needed.
- Studies are needed to assess the performance of prenatal cell-free DNA screening for ADPKD.
- An international registry of women with ADPKD who become pregnant is needed.
CHAPTER 9. PEDIATRIC ISSUES

Appropriate interventions for children with and those at risk for ADPKD are lacking as there are currently no validated stratification models to identify children at risk of rapid progression and no approved therapies specifically for this population.\textsuperscript{651, 652} Therefore, this chapter aims to harmonize current practices for care of children with, or at risk for, ADPKD and to highlight the gaps and the future perspectives in the pediatric ADPKD research field.

9.1. Diagnosis of ADPKD in children

Practice Point 9.1.1: ADPKD may begin in early childhood or antenatally, although clinical symptoms are rarely perceived early in life. VEO-ADPKD and early onset (EO-ADPKD) forms of ADPKD are rare and distinct subentities of ADPKD (Table 15).

<table>
<thead>
<tr>
<th>Subentity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEO-ADPKD</td>
<td>Symptoms or clinical evidence of severe ADPKD under 18 months of age defined by:</td>
</tr>
<tr>
<td></td>
<td>● antenatal diagnosis of hyperechogenic enlarged kidneys (&gt;2 SD for gestational age) with oligohydramnios, OR</td>
</tr>
<tr>
<td></td>
<td>● enlarged cystic kidneys (&gt;2 SD for age, sex, height) between birth and 18 months of age with hypertension (BP ( \geq 95^{th} ) percentile for age, sex, and height) and/or decreased eGFR</td>
</tr>
<tr>
<td>EO-ADPKD</td>
<td>Symptoms or clinical evidence of severe ADPKD between 18 months and 15 years of age determined by:</td>
</tr>
<tr>
<td></td>
<td>● presence of enlarged cystic kidneys (&gt;2 SD for age, sex, and height) between 18 months and 15 years of age with hypertension (BP ( \geq 95^{th} ) percentile for age, sex, and height) and/or decreased eGFR</td>
</tr>
<tr>
<td>Child with ADPKD</td>
<td>A child with diagnosis of ADPKD not fulfilling VEO-ADPKD or EO-ADPKD criteria</td>
</tr>
<tr>
<td>Child at risk of ADPKD</td>
<td>A child in a family with ADPKD and at-risk</td>
</tr>
</tbody>
</table>

Table 15. Definitions of phenotypical entities in children with autosomal dominant polycystic kidney disease (ADPKD). BP, blood pressure; eGFR, estimated glomerular filtration rate; EO, early onset; SD, standard deviations; VEO, very early onset

It is widely accepted that ADPKD starts early in childhood or even antenatally.\textsuperscript{653} A wide variability of phenotypical ADPKD presentations exists early in life. Rarely, children present with severe clinical features mimicking ARPKD including enlarged, cystic kidneys with oligo- or anhydramnios and pulmonary hypoplasia, arterial hypertension, and/or a decreased GFR after birth. Most people with early detected ADPKD present with kidney cysts in childhood and adolescence.\textsuperscript{60, 61, 654-658}
No validated definition of disease progression in children with ADPKD is available, VEO-ADPKD and EO-ADPKD entities have been proposed in the 1990s and 2000s. These definitions do not reflect the concept of genetic modifiers or mutational load, and different studies applied different criteria for VEO-ADPKD and EO-ADPKD. VEO-ADPKD has been described as ADPKD diagnosed in utero with hyperechogenic enlarged kidneys (>2 SD for gestational age) with oligohydramnios or between birth and 18 months of age with enlarged cystic kidneys (>2 SD for age, sex, height) with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR. EO-ADPKD has been described as ADPKD diagnosed between 18 months and 15 years of age with enlarged cystic kidneys (>2 SD for age, sex, and height) between 18 months and 15 years of age with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR. It has been described that children with VEO-ADPKD were more likely to develop hypertension and to progress to an eGFR <90 ml/min per 1.73 m² by adolescence compared to people with ADPKD diagnosed during childhood. The very severe phenotypes in early childhood are often due to combinations of mutations in 2 or more ADPKD genes, and therefore very rare (Chapter 1).

Practice Point 9.1.2: Shared decision-making and a family-centered approach should be undertaken when discussing the benefits and harms related to diagnosis of at-risk children in families with ADPKD, including the parents/legal guardians and the mature child (Chapter 1; Figure 51).

Practice Point 9.1.3: Offer expert counseling about potential diagnostic options by a multidisciplinary team including a pediatric nephrologist and a geneticist with expertise in ADPKD to families with children at risk for ADPKD.

The request for counseling by families with children at risk for ADPKD is increasingly prevalent as more data on children with ADPKD are emerging. There are multiple complex issues to be considered in a counseling situation concerning a typically slowly-progressing, genetically dominant disorder, including medical, psychological, cultural, ethical, socioeconomic, and legal aspects. Approaches may vary according to the cultural background of the family, the family’s beliefs, wishes, and preferences, family history, and the healthcare system in which the counseling takes place. Moreover, the symptomatology and the potential psychosocial aspects of either a diagnosis of ADPKD or being at risk of ADPKD can be complex for children and adolescents. We advise a shared decision-making and family-
centered approach in discussing the potential benefits and harms related to diagnosis of children at risk for ADPKD, which includes the parents or legal guardians and the mature child. In younger children, information should be offered in an age-appropriate way. It is of utmost importance to be aware of the possible different clinical courses of ADPKD, the specific psychosocial implications of early diagnosis for a child and the family, as well as the potential clinical benefits and consequences of early diagnosis. Thus, counseling and empowerment of families on potential diagnostic steps in children at risk of ADPKD should be performed by a multidisciplinary team, including a pediatric nephrologist and geneticist with expertise in ADPKD.\textsuperscript{367,660} Guidelines for diagnosing ADPKD provide a consensus framework to approach children and adolescents with symptoms of or at risk of ADPKD.\textsuperscript{367,660}

**Practice Point 9.1.4:** When diagnosis of ADPKD in children is desired, use ultrasound as the preferred imaging method.

**Practice Point 9.1.5:** Inform people and families that the presence of a single kidney cyst in a child with a positive familial history of ADPKD is highly suspicious for the diagnosis of ADPKD (Figure 50).

**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 (Figure 50).

**Practice Point 9.1.7:** In children with kidney cysts and negative family history for ADPKD who seek diagnosis, perform ultrasound of the parents (or grandparents if parents <40 years) (Figure 50).

**Practice Point 9.1.8:** Consider a simple cyst as a differential diagnosis in children with an isolated cyst, negative family history, and negative ultrasound workup of the parents (or grandparents if parents <40 years).
Figure 50. Diagnosis of children with suspicion of autosomal dominant polycystic kidney disease (ADPKD). *Consider screening grandparents if parent screening is negative or parents <40 years of age. †e.g., very early onset ADPKD, significant kidney involvement. ADPKD, autosomal dominant polycystic kidney disease; VEO, very early onset

Ultrasound remains the preferred method of diagnosing and following children with ADPKD as it is cost-effective, painless, widely available, does not require radiation or sedation, and has a high diagnostic sensitivity and specificity. The detection of even a single cyst in children <15 years with a positive family history of ADPKD is highly suspicious for ADPKD, as the incidence of simple cysts in childhood and adolescence is low.

Ultrasound examination of the parents of children with kidney cysts and negative family history should be performed as a first step. Ultrasound findings in parents will help to find the correct diagnosis for children as they give information on the mode of inheritance. Ultrasound of a grandparent may be helpful in a situation where parents are <40 years of age given the fact that in people with mild ADPKD ultrasound may not show cysts in people <40 years (Chapter 1). Families should be counseled that a negative ultrasound finding (no cysts seen) in children and adolescents does not rule out ADPKD.

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.
Figure 51. Diagnosis of children at risk of autosomal dominant polycystic kidney disease (ADPKD).
*See Table 3 in Chapter 1.

Offering genetic testing by state-of-the-art massive parallel sequencing techniques should be suggested for children with VEO-ADPKD, atypical courses, or atypical presentation or imaging of ADPKD, and in children with cystic kidneys and a negative familial history of ADPKD (Chapter 1). Biallelic or monoallelic variants in PKD genes with a high prevalence of PKD1 variants have been identified in people with VEO-ADPKD and a severe phenotype. Genetic testing should adequately cover PKD1 as described in Chapter 1. Furthermore, multiple additional genes for cystic kidney disease phenotypes for which analysis in a panel should be considered is presented in Chapter 1 of this guideline.

9.2. BP control in children and adolescents with ADPKD
Practice Point 9.2.1: Assess standardized office BP annually in children and adolescents with and at risk for ADPKD.
Practice Point 9.2.2: In children and adolescents (≥5 years and height ≥120 cm) with ADPKD and office BP ≥75th percentile for age, sex, and height, perform annual 24-hour ABPM in accordance with recommendations on BP targets in pediatric CKD. In children and adolescents (≥5 years and height ≥120 cm) with VEO-ADPKD or EO-ADPKD, perform annual 24-hour ABPM.

Practice Point 9.2.3: If ABPM is not available, routine in-office or HBPM are acceptable alternatives.

Practice Point 9.2.4: Evaluation of high BP in children and adolescents with or at risk for ADPKD should consider the possibility of primary or other secondary causes.

High BP (defined as BP ≥95th percentile for age, sex, and height, or ≥130/80 mm Hg in adolescents) affects 20%–40% of children and adolescents with ADPKD, increases with age, and is more prevalent than in the general pediatric population (<5%). Several lines of evidence support the importance of early detection and rigorous treatment of high BP in children and adolescents with ADPKD. A positive correlation between BP and total kidney and cyst volume by ultrasound and MRI has been consistently observed in children and young adults with ADPKD between 4–22 years of age, a finding similar to older adults with ADPKD. Children with ADPKD and BP in the high normal range (75th–95th percentile) or with BP <75th percentile but with ≥10 kidney cysts by ultrasound have high risk to develop high BP within the subsequent 5 years. Moreover, children with ADPKD and high BP experience faster kidney growth and decline of kidney function compared to their normotensive peers. As high BP is the primary treatable disease manifestation of ADPKD in childhood, routine monitoring of BP should be performed at least annually from birth in children and adolescents diagnosed with or at risk for ADPKD.

Children and adolescents with ADPKD and BP in the high normal range (75th–95th percentile for age, sex, and height) presumably are at increased risk of kidney and CVD in later life compared to those with lower BP. LVMI is elevated in children and adolescents with ADPKD and high normal BP and is comparable to those with high BP. Additionally, over 50% of affected children and adolescents with high-normal BP will develop high BP in a subsequent 5-year follow-up period. Therefore, more detailed BP assessment is indicated in children and adolescents with ADPKD with BP above the 75th percentile. For children at-risk of ADPKD with BP ≥75th percentile for age, sex, and height, a yearly follow-up is particularly important to identify high BP early and to discuss potential next diagnostic steps with parents in a timely way.

When available, 24-hour ABPM can be utilized in children ≥5 years old and ≥120 cm in height and is the preferred modality to diagnose high BP and to evaluate antihypertensive
efficacy in children. ABPM is a better predictor of target organ damage than office BP measurement in adults and has been shown to better target therapeutic goals in high-risk pediatric populations, including CKD. Major advantages of ABPM include evaluation for white coat hypertension and assessment of circadian BP patterns. A significant proportion of children and adolescents with ADPKD manifest isolated nocturnal hypertension or non-dipping pattern which requires treatment but would not otherwise be identified by office BP measurement. Indeed, isolated nocturnal hypertension with normal daytime BP has been observed in 16%-18% of children with ADPKD. Monitoring frequency by ABPM will depend on local availability, level of clinic or home BP, and/or use of antihypertensive therapy. However, similar to guideline recommendations in children and adolescents with CKD, an ideal approach is to consider routine ABPM in children and adolescents with ADPKD with office BP ≥75th percentile for age, sex, and height, with annual ABPM in the setting of established high BP. Given the particularly high frequency of high BP and risk of progressive abnormal kidney function in children and adolescents with VEO- and EO-ADPKD, a more comprehensive assessment for high BP is indicated in these subgroups and would ideally be undertaken with annual ABPM, particularly with BP ≥75th percentile. Guidelines for appropriate application of ABPM in childhood have also been published. If ABPM is not available, routine office or HBPM are acceptable alternatives.

Careful evaluation for potential etiologies and contributors to BP elevation is indicated in children and adolescents with ADPKD or at risk of ADPKD and high BP, as other secondary etiologies (e.g., renal artery stenosis, aortic coarctation) or primary hypertension may be relevant. In children and adolescents in whom high BP appears to be related to ADPKD, dietary and exercise interventions are still important management factors to help modulate long-term cardiovascular risk. In children and adolescents who are at risk for ADPKD, a kidney ultrasound should be obtained in the setting of high BP in order to support comprehensive evaluation in the setting of family history of kidney disease, guide best treatment practices and anticipated outcomes, and better define long-term kidney and cardiovascular risk. The potential outcomes, benefits, and risks of kidney ultrasound should be discussed with the mature person with ADPKD and parent/guardian in this setting prior to performing the examination.

Practice Point 9.2.5: Echocardiography should be performed to exclude left ventricular hypertrophy (LVH) in children and adolescents with ADPKD and high BP.

Children and adolescents with ADPKD are more likely to have increased LVMI as compared to healthy children and adolescents at equivalent BP, and there is good correlation between both systolic and diastolic BP and LVMI in children and adolescents with ADPKD, even within the normal BP range. Importantly, children and adolescents with ADPKD and BP in the high-normal range demonstrate an increase in LVMI which is similar to that of children and adolescents with ADPKD and high BP and is significantly higher than that of affected
children with BP <75th percentile. These observations suggest that children and adolescents with ADPKD may be at risk for early onset cardiovascular complications. Therefore, the Work Group advises that an echocardiogram be performed in children and adolescents with ADPKD and high BP. The frequency of follow-up echocardiography will be impacted by initial findings, BP values, and the degree of control of high BP if present. The finding of LVH will reinforce the need for rigorous BP control and lead to more frequent follow-up echocardiography to ensure that LVH appropriately resolves.

**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 (ID).

This recommendation places a high value on the potential benefits of rigorous control of high BP for slowing progression of kidney and CVD progression in children and adolescents with ADPKD while recognizing that this approach may result in more antihypertensive exposure for young people with ADPKD and increased risk of potential side effects (e.g., lightheadedness, dizziness, with ADPKD and potentially increased risk of side effects (e.g., lightheadedness, dizziness, psychological effects of having to take several pills every day, others).

**Key information**

*Balance of benefits and harms*

Studies in pediatric CKD G2–G4 support aggressive control of high BP to mitigate progressive loss of kidney function over time, and the HALT-PKD clinical trials demonstrated slowing of TKV growth in adults with ADPKD managed with rigorous control of high BP. As noted previously, there is a consistent and strong correlation between BP and TKV in children and young adults with ADPKD throughout the normal range of BP, as well as elevation in LVMI beginning in children with ADPKD with BP exceeding the 75th percentile. Based on these findings, a target BP of ≤50th percentile for age, sex, and height or ≤110/70 in adolescents appears appropriate in this pediatric population at high long-term risk for CKD and CVD. As was observed in the HALT-PKD clinical trial, a more rigorous BP goal could be associated with increased occurrence of potential side effects (lightheadedness, dizziness, etc.). These risks should be discussed in advance with people with ADPKD and families before providing intervention and reviewed as treatment proceeds.

*Certainty of evidence*

Multiple studies in children and adolescents with ADPKD have confirmed a strong positive correlation between high BP and TKV. A single small trial, with serious methodological limitations (due to high dropout rates and lack of participant blinding), compared BP targets. No studies in children and adolescents have compared different antihypertensive regimens. The certainty of evidence for rigorous BP targets in children and adolescents with ADPKD and high BP was deemed very low (Level D).
Values and preferences

Limiting the rate of progression to kidney failure and other complications of ADPKD is critically important to people with ADPKD. It has been proposed that earlier intervention (i.e., in childhood) may be of particular benefit to long-term clinical outcomes in ADPKD. Blood pressure can be easily monitored with appropriate therapy adjustments made. Given these considerations, the Work Group surmised that most, if not all, people with ADPKD (or parents/guardians of children with ADPKD) would choose to provide more rigorous BP control as an intervention, while accepting the potential need for more frequent BP monitoring and/or potential medication side effects.

Resource use and costs

More frequent BP assessment in the form of in-office or HBPM may be required in this setting. Increased use of antihypertensive medication may be needed to reach the target BP goal.

Considerations for implementation

Education of individuals and caregivers is important to outline appropriate therapeutic goals and to mitigate side effects. Local resources should be utilized to provide appropriate BP monitoring.

Rationale

Control of high BP has been shown to delay the progression of kidney disease in children, and studies in adults have demonstrated an association of BP control to slow growth of TKV in people with ADPKD. However, this approach may result in increased and earlier exposure of children and young people to antihypertensive therapies and their potential side effects. Still, given the potential benefits in people with ADPKD, including the potential to lower the risk of CKD and CVD in the long-term, the Work Group recommends a BP target of ≤50th percentile for age, sex, and height in children or ≤110/70 mm Hg in adolescents.

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

This recommendation places a high value on the potential benefits of high BP treatment with RASi over other types of antihypertensive agents for slowing progression of abnormal kidney function and CVD in children and adolescents with ADPKD, while it places a relatively lower value on the potential side effects and other risks of these medications.

Key information

Balances of benefits and harms
Blockade of the RAS is often the preferred mechanism for management of high BP in pediatric CKD G2–G4 and has been proposed to have particular value in high BP management in ADPKD. Mechanistically, excessive activation of the RAS by kidney cyst expansion is felt to be a primary contributor to high BP. Although less is known in children and adolescents with ADPKD, the pathophysiology is believed to be similar to that of adults.\(^68^{1}\) RAS blockade has a valuable role in mitigating glomerular hyperfiltration, a common and early feature of ADPKD in children and adolescents.\(^68^{2}, 68^{3}\) Targeting 50\(^{th}\) percentile BP using RASI in children and adolescents with ADPKD and high normal BP (75\(^{th}\)–95\(^{th}\) percentile) has been shown to limit eGFR decline and LVMI increase as compared to conservative monitoring.\(^16^{0}\) Although there are no studies comparing different antihypertensive regimens in children and adolescents with ADPKD, the Work Group agreed that blockade of RAS with ACEi or ARB should be the preferred agents for management of BP in this group. These medications are widely utilized with good efficacy and reassuring side effect profile in many children and adolescents with high BP, proteinuria, and/or glomerular hyperfiltration including those with ADPKD.\(^16^{0}, 68^{4}-68^{7}\)

**Certainty of evidence**

The certainty of evidence for choice of antihypertensive in children and adolescents with ADPKD was very low (Level D) due to sparseness of evidence (Supplementary Table S3, S4, and S21).

**Values and preferences**

Limiting the rate of progression to kidney failure and other complications of ADPKD is critically important to people with ADPKD. It has been proposed that earlier intervention (i.e., in childhood) may be of particular benefit to long-term clinical outcomes in ADPKD. Moreover, ACEi or ARBs have been widely used in children and adolescents for conditions such as high BP, proteinuria, and glomerular hyperfiltration, with experience showing that associated routine monitoring of BP, kidney function, and electrolytes is feasible and not intrusive in routine clinical practice. Given these considerations, the Work Group, therefore, surmised that most, if not all, people with ADPKD or parents/guardians of children with ADPKD would choose to utilize ACEi or ARBs in the appropriate clinical setting. There is no current evidence to support the use of ACEi over ARBs or vice versa in children and adolescents with ADPKD. The choice of medication will depend on factors such as patient preference, expense, drug availability including commercial suspension availability for young people who cannot swallow tablets, side effect profiles of individual drugs, and local prescribing experience. ACEi-induced cough can affect up to 10% of people taking these medications.

**Resource use and costs**

Generic formulations of ACEi and ARBs are available throughout the world. Some ACEi and ARBs are available commercially in liquid form to facilitate oral uptake in children or have standardized procedures to compound into liquid form.
Consideration for implementation

ACEi or ARB can cause hypotension, hyperkalemia, and increased SCr in addition to other established side effects. It is therefore reasonable to periodically monitor BP, electrolytes, and kidney function in young people receiving these medications. The risk of acute decrease in eGFR is of particular concern in people with renal artery stenosis or eGFR below 30 ml/min per 1.73 m². These medications can cause adverse developmental effects in the fetus and should be avoided during pregnancy. Parents/guardians and females (as developmentally appropriate) should be counseled regarding this risk. Such medications should be provided by prescribers with experience in their use. The impact of routine use of RASi on LVMI in children with ADPKD and high BP remains to be seen and may ultimately affect best practices for the frequency of echocardiography in this population.

Rationale

Managing high BP in children and young people has been shown to lower the risk of CKD and CVD in the long-term. BP control also has been shown to be beneficial for the management of ADPKD; however, studies examining the impact of different antihypertensive therapies in children and young people have not yet been performed. Still, these drugs have been used in children and young adults with conditions other than ADPKD and have been shown to have a positive efficacy and safety profile. They are also widely available and generally low cost. Therefore, if antihypertensive therapy is needed to control high BP in children and young people with ADPKD, the Work Group recommends RASi as first-line pharmacological therapy.

Practice Point 9.2.6: High BP should be managed by a pediatric nephrologist or other local expert.

Pediatric nephrologists are uniquely qualified to manage high BP in children with ADPKD and, when available, should have primary responsibility for this aspect of management.

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 (Figure 52).

Due to the wide range of clinical findings in children with ADPKD, the frequency of monitoring should be individualized based on the severity of clinical features, degree of BP control, and laboratory (e.g., kidney function, electrolytes, urinalysis for hematuria/proteinuria, urine protein-to-creatinine ratio) and ultrasound findings. Indeed, early identification and
management of factors that may modify disease progression, such as high BP, are of most importance for young children with ADPKD.\textsuperscript{688}

**Figure 52.** Follow-up of children with autosomal dominant polycystic kidney disease (ADPKD). ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; EO, early onset; NSAID, nonsteroidal anti-inflammatory drug; VEO, very early onset

**Practice Point 9.3.2:** Do not perform routine screening for extrarenal manifestations including liver, pancreas, or spleen cysts; cardiac valvular disease; and ICA in children and adolescents with ADPKD (Figure 52).

**Practice Point 9.3.3:** Assessment of extrarenal manifestations is required only when there are concerning symptoms or to differentiate the findings from other cystic kidney diseases (Figure 52).

Hepatic cysts are observed in <4% of children with ADPKD, with no cases of significant liver disease described.\textsuperscript{644, 657, 671} The prevalence of pancreas or spleen cysts in children with ADPKD is not known but is believed to be even less common than adults. Therefore, routine
screening is not indicated in childhood. However, screening for liver or pancreas involvement may be helpful if the clinical findings require differentiation from other cystic kidney diseases such as ARPKD, atypical forms of ADPKD (e.g., due to pathogenic variants in GANAB, ALG9), HNF1β nephropathy, or in the cases of concerning symptoms.

Although earlier studies suggested a higher risk for cardiac valve disease in children with ADPKD, more recent studies have shown low frequency. Therefore, screening for cardiac valvular disease should be pursued only when there is a concerning cardiac examination. ADPKD-associated ICA are exceedingly rare in childhood, and routine screening is not necessary.

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: Manage abdominal pain in children with ADPKD the same as for children without ADPKD including an abdominal ultrasound. Use of nonsteroidal anti-inflammatory agents (NSAIDs) should be avoided or used sparingly for only a few days when absolutely needed.

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

UTIs are a common cause of fever in children. Studies have reported an increased incidence of UTIs for children with ADPKD, but concerns of potential bias have been raised. There are no reports of increased incidence of severe UTIs in children with ADPKD. Thus, general principles of UTI diagnosis and treatment apply, including urinalysis, urine culture, and possible blood tests, and ultrasound. Treatment of UTI should follow local recommendations according to resistance spectra. Minimization of use of nephrotoxic agents in the treatment should be considered, particularly in children with VEO-ADPKD and EO-ADPKD, as clinically possible.

Cyst infection is rare in children with ADPKD and no specific recommendations can be given for this population. Cyst infection should be considered and diagnostic assessment beginning with an ultrasound examination should be initiated in people with atypical courses of UTIs (e.g., unresponsive to standard treatment or untypically severe clinical presentation).
Abdominal pain is common, affecting 10%–20% of children with ADPKD.\textsuperscript{367, 643, 690} Evaluation and treatment should be tailored according to the clinical picture. The local standard evaluation of abdominal pain in childhood and adolescence should be followed first. Frequent use of NSAIDs should be avoided due to the underlying kidney disease, and multidisciplinary treatment of chronic pain should also be initiated early in children and adolescents.\textsuperscript{367}

Clinical evaluation of suspected nephrolithiasis should be performed in the same way as in healthy children, including an analysis to look for hypocitraturia. Ultrasound is the preferred imaging modality to look for kidney stones.

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

The prevalence of proteinuria was 20% in children with ADPKD in a recent meta-analysis.\textsuperscript{672} Concerns have been raised that this may be influenced by a selection bias in the documenting centers. However, proteinuria is an established and treatable risk factor for progression of CKD in children.\textsuperscript{677, 694} ACEi and ARBs are recommended for proteinuria in children with CKD.\textsuperscript{157} The same principles apply for evaluation and treatment of proteinuria in ADPKD as for children with other underlying kidney diseases. Measuring albumin-to-creatinine ratio in a laboratory has been prioritized over dipstick testing. Orthostatic proteinuria should be excluded.

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

Urinary concentrating ability is decreased from childhood in people with ADPKD, potentially contributing to enuresis.\textsuperscript{671} There are no data on particular risks associated with desmopressin treatment but given the known effects of vasopressin antagonists on cyst growth and GFR loss in adults with ADPKD, use of vasopressin analogues should be avoided whenever possible in children with and at risk of ADPKD. Other treatment options should be sought in children with nocturnal enuresis should be sought in children with enuresis and ADPKD.\textsuperscript{367, 695}

\textbf{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.}

While isolated kidney cysts are rare in children,\textsuperscript{667} the studies on incidence and prevalence were mainly performed in the 1980s and 1990s.\textsuperscript{367} Novel ultrasound technology may be more sensitive in identifying small cysts leading to an increase in detection of isolated simple kidney cysts in children. BP measurements in these children should be obtained at least once yearly.
Ultrasound imaging can be repeated every 3 years. Complicated cysts are very rare in children but atypical ultrasound cyst findings require more extensive diagnostic work-up as suggested in Gimpel et al.\textsuperscript{696}

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 (Figure 52 and 53).

![Flowchart](image)

**Figure 53. Follow-up of children at risk for autosomal dominant polycystic kidney disease (ADPKD).** ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; NSAID, nonsteroidal anti-inflammatory drug

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.

High body weight and obesity have been identified as independent risk factors for disease progression in adults with ADPKD.\textsuperscript{119, 563} No studies evaluated the impact of BMI on
progression of ADPKD in children. Nevertheless, childhood obesity is associated with obesity in later adulthood and subsequent cardiovascular complications. Furthermore, high BMI and obesity have been linked with the occurrence of CKD, hypertension, and the development of metabolic syndrome. A healthy lifestyle with regular exercise, avoidance of smoking, avoiding nephrotoxic drugs, a healthy diet with appropriate caloric and fluid intake should be advised from early stages ADPKD and a normal BMI should be promoted from childhood.

Dietary regimen with low protein intake or caloric restriction should not be implemented in the growing child. Children with ADPKD should follow general recommendations for a healthy diet, consistent with WHO guidelines and should maintain a healthy body weight. Children with ADPKD and hypertension or CKD should follow the diet according to the guidelines for all children with hypertension or CKD. Previously held beliefs on avoidance of contact sports participation related to risk of cyst bleeding are rarely relevant. However, inform the child or guardian of the risk of direct trauma during contact sports due to relative/absolute nephromegaly. If a particular sport or physical activity is repeatedly followed by gross hematuria, that activity should be avoided.

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.

There are established approaches for pediatric-to-adult transition for children affected by kidney disease. While most that have been reported are in a kidney transplant setting, there are encouraging reports of structured and successful transition programs in nontransplant settings as well. The importance of a planned transition for those affected by ADPKD and other cystic kidney disease is increasingly apparent. National descriptions of pediatric to adult transition experiences, systems, and pathways further reinforce these observations and the importance of multidisciplinary constructs within these programs. Since there is not a standard or consensus approach to transition from pediatric to adult nephrology, the transition should be individualized to unique patient, family, and clinical settings (Figure 54).
Figure 54. Suggested autosomal dominant polycystic kidney disease (ADPKD) transition scheme.

At this important clinical care juncture point, we note that family planning and extrarenal manifestations become of increased importance (Chapters 6 and 8). Further, as ADPKD is a relatively common, slowly progressive disease, transitioning children need not necessarily be managed at a specialized ADPKD center, but caregivers are encouraged to maintain knowledge of active research studies and novel therapies, and share potential opportunities for involvement with these young people as appropriate. This may involve encouraging engagement with patient support organizations or groups as is suggested for other people with ADPKD (Chapter 10).

**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.**

It is not infrequent for nephrologists to be asked by people with ADPKD regarding how they might discuss ADPKD with their children or grandchildren.\(^{595,663}\) While potentially confronting, this is an opportunity to empower people with ADPKD and their families in openly discussing the condition in a manner that they feel is appropriate to their situation or scenario.\(^{708}\) Furthermore, it can support affected parents and grandparents in sharing their experiences with others for both personal and family potential benefits. It may be appropriate to provide information directly and/or refer to ADPKD centers of expertise to provide advice if indicated. In some situations, it may be appropriate to include a pediatric nephrologist in the discussion, if possible, or to anticipate some broad areas of concern such as diagnostic methods, treatment, complications, and prognostication. While no two clinical scenarios in this setting will be exactly alike, it is appropriate to adopt an open approach that does not engender fear or alarm but rather is informative and supportive.

**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.**

There is insufficient evidence for the use of any targeted or disease-modifying treatments for ADPKD in affected children at this time such as tolvaptan;\(^{652,709,710}\) although a single RCT, has indicated tolerability and suggests potential effect on annual TKV expansion.\(^{310}\) A trial of
Curcumin did not show benefit in children affected by ADPKD.\textsuperscript{711} However, a single trial on children and young adults with pravastatin resulted in a significantly slower increase in hTKV over time as compared to placebo.\textsuperscript{364} Further trials are required. Specific trials are also required before the benefit identified in adults can be definitively extended to affected children in certain scenarios. Children and families might consider enrolling in ADPKD clinical trials if they are eligible. Even though there are few new ADPKD trials anticipated in the near term for those aged <18 years, these should be encouraged. Furthermore, adherence with local medication approvals, regulations, and licensing is indicated, though nuanced situations may occur where individualized consideration within local approval or access pathways might be given to other use of therapeutic agents in children and adolescents.

**Research recommendations**

- Studies are needed to validate the definition of VEO-ADPKD and EO-ADPKD and analysis of its clinical relevance and natural course.
- Studies are needed to evaluate the most accurate method of estimating GFR in children with ADPKD.
- Research is needed to better understand the natural disease course (including the course of eGFR) in children with ADPKD.
- Research is needed to assess the prevalence of proteinuria in children with ADPKD and at what age and in which subgroups proteinuria is detected.
- An evaluation should be conducted to best define rapid disease progression in children with ADPKD.
- Studies are needed to assess the role of obesity for rapid progression of ADPKD in childhood.
- Studies are needed to examine the value of additional genetic variants on the prognosis of children with ADPKD.
- Studies are needed to assess the impact of early and aggressive treatment of hypertension during childhood on ADPKD disease progression at later age.
- Studies are needed to determine whether the yearly growth of kidney volume is important for the follow-up of disease progression in children with ADPKD.
- Studies are needed to evaluate the relevance of statins for TKV growth in children.
- Research is needed to assess which group of children with ADPKD are the best candidates for clinical trials.
- Studies are needed to assess the updated and validated consensus approach(es) to pediatric-to-adult transition within nephrology, specifically in regard to ADPKD.
CHAPTER 10. APPROACHES TO THE MANAGEMENT OF PEOPLE WITH ADPKD

ADPKD is a systemic, multi-organ chronic condition in which diagnosis, management, treatment, and lifelong care needs expertise from different medical specialties. People presenting with the disease will usually need to see a range of specialized health care providers during their lives. Inconsistencies or gaps in their care can lead to frustration and uncertainty about whether they are getting the best possible care. The management of people with ADPKD proposed below is based on evidence from the care of people with other complex, syndromic and/or rare conditions. There is no evidence that people with ADPKD should be treated differently.

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

Shared decision-making is an approach where clinicians and patients share the best available evidence and where people are supported to consider options and make informed decisions (Figure 55). This collaborative process may deal with care that the person needs straightaway or care in the future, for example, through advance care planning. It involves choosing tests and treatments based both on evidence and on the person’s individual preferences, beliefs, and values. It means that the person should understand the risks, benefits, and possible consequences of different options through discussion and information-sharing. This joint process empowers people to make decisions about the care that is right for them at that time, including the options of having no treatment or not changing what they are currently doing. 712, 713
Figure 5. The SHARE approach for shared decision-making. Reproduced from The SHARE Approach: A Model for Shared Decisionmaking - Fact Sheet accessed at https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/factsheet.html

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

Care pathways are structured multidisciplinary care processes used to standardize care, reduce variation, equalize access, improve quality of care, and maximize patient outcomes in a specific population. Care pathways interpret guidelines and other recommendations for local/regional/national implementation and take account of care transitions (e.g., from pediatric to adult care, early CKD to kidney failure or conservative care). The implementation of such pathways needs to consider local organization of services, available competencies and resources, and healthcare provider structures and care systems. A comprehensive approach means including or dealing with all elements of ADPKD (i.e., non-kidney as well as kidney manifestations, including mental health considerations) as well as research perspectives (Figure 56). Holistic means treating the person as a whole, considering mental and social factors, rather than just physical symptoms.

Early diagnostic and prognostic assessment led by a nephrologist is advised. Assistance from centers of expertise (also designated as specialized centers or centers of excellence/reference in some jurisdictions) may optimize monitoring and treatment of extrarenal complications. Shared decision-making with primary care physicians or comanagement with other nephrologists (e.g., coupled with remote case-conferences) should be considered for long-term follow-up.
The timing of each assessment or investigation and the need to refer for specialist advice will depend on the individual person. The composition of the multidisciplinary care team needs to be adjusted to the renal and extrarenal manifestations of the disease which vary widely from person to person and their severity of CKD which may determine the goals of specific therapies.

In settings where access to medical care is limited by resource or location, new technologies, such as telehealth, could be considered. A systematic review concluded that eHealth self-management interventions have the potential to improve disease management and health outcomes in CKD, but barriers remain, and more research is needed in ADPKD.

For a detailed discussion of prognostic assessment in ADPKD, please refer to Chapter 1.

![Figure 56. A proposed autosomal dominant polycystic kidney disease (ADPKD) care pathway.](image)

**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).

The key to future therapeutic innovation in ADPKD will be through enabling and facilitating active participation of people with ADPKD. Thus far, the evidence base for decision-making about most clinical interventions in ADPKD is of low or very low strength – reflecting the lack of sufficiently powered studies. Historically, trials in ADPKD have adopted a disparate array of outcome measures. Initiatives such as the SONG-PKD are establishing a codesigned set of outcomes with involvement of all stakeholder groups. In addition, emerging and patient-
centered measures for key outcomes, such as pain, are critical to the success of future trials.\textsuperscript{175} Given the array of emerging trial opportunities, collaborative and innovative clinical trial designs should be considered, such as platform trial approaches, to optimize the ability of people with ADPKD to participate whilst also delivering cumulative research efficiency and expedited outcomes.\textsuperscript{722, 723} The incorporation of such trial approaches with patient registries and cohort studies will additionally assist with refinement of diagnostic criteria, prognostication, and understanding of the biology and natural history of ADPKD.

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

The availability of genetic testing for people with ADPKD is increasing, with established diagnostic and prognostic values (Chapter 1). Integration of genetics into the multidisciplinary team taking care of people with ADPKD has now been implemented successfully in many locations. The increased access to genetic testing and the complexity of the matter render necessary to ensure that nephrologists and other health care providers have relevant literacy in terms of genetics and genetic testing.\textsuperscript{724} Appropriate education and training on the benefits and aims of genetic testing should be provided through multidisciplinary clinics, within the context of referral to centers of expertise, and with relevant focus on ADPKD.

**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.**

As in other genetic disorders causing multisystemic complications, the care pathways in ADPKD may be complex and may need to involve care coordination or multiple care providers.\textsuperscript{725} Although the majority of people with ADPKD present in adulthood, the need for coordination can be especially challenging at healthcare transition stages. Care coordinators or patient navigators can be any health or social care professional, or a patient organization commissioned for that purpose. In most people with ADPKD, the nephrologist oversees the nephrology and overall care. The patient and nephrologist may benefit from the assistance of care coordination (or patient navigation), helping to facilitate sometimes stressful and costly interactions with other care providers.\textsuperscript{726}

**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.**

Chronic disease self-management by people is increasingly being viewed as essential to improve health behaviors, health outcomes, and QoL.\textsuperscript{727} Self-management is considered a specific component in the optimal care model in CKD.\textsuperscript{179} There is also evidence from the
Chronic Disease Self-Management Program (CDSMP) that in some conditions, for example diabetes, self-management has proved effective for reducing healthcare utilization and the societal cost burden.\textsuperscript{727} Principles of effective self-management are summarized in Figure 57.

Self-management in CKD is gaining attention as an approach to help reduce CKD progression and prevent complications.\textsuperscript{728} We note, however, that there is a lack of specific self-management education programs that have been shown effectiveness and cost-effectiveness for people with ADPKD.

![Figure 57. Principles of effective self-management.\textsuperscript{728} Please refer to Chapter 7 for more details on lifestyle and psychosocial care of people with autosomal dominant polycystic kidney disease (ADPKD), and the role of self-management programs. Reproduced from Lightfoot CJ, Nair D, Bennett PN, \textit{et al.} Patient Activation: The Cornerstone of Effective Self-Management in Chronic Kidney Disease? Kidney Dial 2022; 2: 91-105. HCPs, healthcare providers]

\textbf{Practice Point 10.7: Healthcare systems should promote the participation of people with ADPKD to registries to gather outcome data using standardized data definitions.}

Registries already exist in many countries that collect and audit data on people on dialysis or with a kidney or liver transplant. A few registries, such as the UK National Registry of Rare Kidney Diseases (RaDaR) or the ERKNET Registry in EU, collect data for genetic kidney diseases across all severities of CKD. Healthcare systems not currently collecting data on people with ADPKD should consider setting up their own registries or collaborating with existing registries. Interoperability between registries should be promoted.

Common data elements for ADPKD have been developed utilizing the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format by
CDISC in conjunction with the U.S. Critical Path Institute, Polycystic Kidney Disease (PKD) Outcomes Consortium, and the U.S. PKD Foundation.\textsuperscript{729} The SDTM allows for electronic submission to regulatory agencies.

Examples of ADPKD-specific registries that have been established, include:
- ERKNET: [https://www.erknet.org/patients-registry/registry-mission](https://www.erknet.org/patients-registry/registry-mission)
- PKD Foundation: [https://connect.pkdcure.org/adpkd-registry/](https://connect.pkdcure.org/adpkd-registry/)
- UK RaDaR: [https://ukkidney.org/rare-renal/metadata](https://ukkidney.org/rare-renal/metadata) (adults and pediatric)

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

Patient support activities include:
- general education about ADPKD and its manifestations,
- general education about ADPKD inheritance and genetics,
- general education about the treatment of the complications of ADPKD,
- provision of educational sessions by health professionals or patient-leaders,
- participation in mutual patient support groups, especially through peer support, to allow people a greater understanding of day-to-day living with ADPKD,
- support activities that are targeted to the appropriate stage and interest of the audience (e.g., for parents of affected children or for those considering KRT),
- moderation of social media posts in online groups and forums,
- information on sources of financial support and assistance for various aspects of care,
- education of researchers and industry about the burden of ADPKD on patients and families, and their unmet needs,
- involvement in design and development of studies and clinical trials,
- information about opportunities to participate in research studies.

Patient organizations can promote disease awareness and education to influence health policy locally, nationally, and internationally. Examples are campaigning for reimbursement coverage for treatments, improved healthcare provisions, and legal provisions to avoid discrimination for families with a genetic disease, e.g., for insurability. Patient organizations can be helpful in encouraging people to get more care earlier.

Patient organizations should also interact with clinicians, academia, industry, government, and regulatory agencies to promote research, ensure the patient voice/experience is reflected in all aspects of clinical and experimental research, including the development of new treatments and trial designs, and input to health technology assessments.\textsuperscript{5}
Patient organizations exist in multiple countries. A list may be found at [https://pkdinternational.org/membership](https://pkdinternational.org/membership).

**Research recommendations**

- Determine the cost-effectiveness of multidisciplinary care pathways or multidisciplinary team approaches, including the availability of a care coordinator, in ADPKD.
- Determine how multidisciplinary care pathways could best function in low- and middle-income countries.
- Investigate the role of telehealth in delivering ADPKD care, particularly in low- and middle-income countries and for people in remote settings.
- Assess whether models of nephrology-coordinated care are more effective than those without nephrology coordination.
- Assess whether centers of expertise are effective for optimized monitoring and treatment of extrarenal complications.
- Investigate the role of preclinic visit planning tools to help people with ADPKD prepare for their visit, increase involvement, and improve patient-health professional communications.
- Investigate whether, or which, models of self-management in ADPKD are cost-effective.
- Determine the optimal patient-reported outcome measures for use in ADPKD clinical care and audit.
AIM
The aim of this project was to develop an evidence-based clinical practice guideline for the diagnosis, prognosis, monitoring, prevention of disease progression, and treatment in people with ADPKD. The guideline development methods are described below.

OVERVIEW OF PROCESS
These guidelines adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2, S3, and S4), and have been reported in accordance with the Institute of Medicine and Appraisal of Guidelines for Research and Evaluation (AGREE) II reporting checklists. The processes undertaken for the development of the KDIGO 2023 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease are described below.

- Appointing Work Group members and the ERT
- Finalizing guideline development methodology
- Defining scope and the topics of interest for the guideline
- Developing and refining topics for systematic evidence review
- Formulating clinical questions - Identifying Population, Intervention or predictors, Comparator, Outcomes of interest, and other study Design eligibility criteria (PICOD)
- Developing and implementing literature search strategies
- Screening abstracts and retrieving full-text articles on the basis of predefined eligibility criteria
- Creating data extraction forms
- Extracting data and performing critical appraisal of the literature
- Grading the methodology and outcomes in individual studies
- Tabulating data from individual studies into summary tables and performing meta-analysis where appropriate
- Grading certainty of evidence for each outcome across studies, and assessing the overall certainty of evidence across outcomes with the aid of evidence profiles
- Determining the strength of recommendations on the basis of the certainty of evidence and other considerations
- Convening a public review in October 2023
- Updating the evidence review and recommendation statements based on the current evidence and other considerations
- Finalizing and publishing the guideline
Commissioning of Work Group and ERT for the guideline update

KDIGO assembled a Work Group with expertise in ADPKD, adult and pediatric nephrology, hepatology, urology, genetics, epidemiology, public health, and guideline development. The Work Group also included 3 people living with ADPKD. The Work Group was responsible for defining the scope of the guideline, writing the graded recommendations and the underlying rationale, grading the strength of the recommendations, and developing practice points.

The Brown University Center for Evidence Synthesis in Health in Providence, Rhode Island was contracted as the ERT to conduct systematic evidence review and provide expertise in guideline development methodology. The ERT consisted of physician-methodologists with expertise in nephrology and evidence-based clinical practice guideline development, an experienced research associate/medical librarian, and several research associates with experience in systematic review methods. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, critical appraisal, evidence synthesis and meta-analysis, grading the certainty of the evidence per outcome, and grading the overall certainty of the evidence for the recommendations.

Defining scope and formulating key clinical questions

The guideline Work Group, with assistance from the ERT, defined the overall scope, the goals of the guideline, and drafted a preliminary list of topics and key clinical questions. This included a determination about which topics the ERT would address by systematic review. Issues considered to determine topics to be systematically reviewed included specificity of the topic to ADPKD (e.g., tolvaptan treatment vs. prevention of kidney stones or management of dialysis); importance of the topic to the majority of patients, families, and clinicians; prioritization of medications and imaging interventions; likelihood that sufficient evidence exists to inform recommendations, time requirements and available ERT resources; and other considerations.

Details of the PICOD questions are provided with prioritized outcomes noted in Table 16. Outcome prioritization was based on primarily on the Standardized Outcomes in Nephrology–PKD (SONG-PKD) outcome set. We translated SONG-PKD outcome categorization into the structure proposed by Grading of Recommendation, Assessment, Development, and Evaluation (GRADE). SONG-PKD “core” outcomes were preliminarily considered to be of “critical” importance (GRADE rating 7-9), “middle tier” outcomes were considered to be “important but not critical” (GRADE rating 4-6), and “outer tier” outcomes were considered to be “of least importance” (GRADE rating 1-3). The outcomes that were considered for systematic review were tabulated for each topic together with their SONG-PKD categorization. Of note, several outcomes of interest to the Work Group were not addressed by SONG-PKD, including harms (adverse events), nonspecific pain, liver-related outcomes, and dialysis-related outcomes. Several
SONG-PKD outcomes were translated to match outcomes of interest to the Work Group (e.g., depression to psychosocial/mental health outcomes and fatigue and impact on family/friends to QoL). After addition of outcomes not included in SONG-PKD, the outcomes were preliminarily organized by SONG-PKD tiers (core outcomes, middle tier, outer tier). The Work Group and Co-Chairs completed surveys based on the GRADE system of prioritizing importance from 1 (least important) to 9 (most critical). The ERT then assisted the Co-Chairs to determine final prioritization for each topic. Outcomes that were determined to be critical or important but not critical were included in evidence profiles.

All evidence reviews were conducted in accordance with the Cochrane Handbook,\textsuperscript{734} the Agency for Healthcare Research and Quality Evidence-based Practice Center Program Methods Guide,\textsuperscript{735} and guideline development adhered to the standards of GRADE.\textsuperscript{736}
<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/ Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
</tr>
</thead>
</table>
| In the general population, what is the prevalence or incidence of diagnosis of ADPKD, by type or specific genic or allelic grouping? | General population    | ● Country  
● Race/ethnicity  
● Age                                                                 |                                                                           | ● Diagnosed ADPKD prevalence  
● ADPKD diagnosis incidence  
● ADPKD type  
   ○ PKD1-T, PKD1-NT & PKD2 associated ADPKD, No detectable mutations  
   ○ Specific genic or allelic ADPKD categories  
   ○ Very early onset ADPKD (pediatric)  
   ○ Related diagnoses (ADPKD-like disorders that are caused by other than the *PKD1 and* *PKD2* genes) | Nationally representative population samples (or equivalent)               |
| What is the association of tools/algorithms, measures, genetic, and other factors with progression of kidney disease?                  | ADPKD                 | ● Tools, algorithms, other combinations of factors  
   ○ PROPKD, Mayo Imaging Classification, PKD consortium, ADPKD  
Outcomes Model, other models  
   ○ *NOT models that predict effectiveness of treatment* (e.g., TEMPO) |                                                                           | ● Progression of kidney disease  
   ○ Change in kidney function (GFR, eGFR, SCr doubling, GFR slope, etc.)  
   ○ Change in CKD GFR category  
   ○ Incident kidney failure  
     ● Kidney replacement therapy  
     ● CKD G5  
     ● Dialysis (hemodialysis or peritoneal dialysis)  
     ● Kidney transplant  
   ○ Change in htTKV or TKV  
● Cyst count/cyst number                                                             | Longitudinal  
≥1 yr f/up post-baseline  
Multivariable-adjusted  
N ≥30  
Exclude:  
● Conference abstracts  
● Correlation or ANOVA analyses                                                      |
<table>
<thead>
<tr>
<th>Clinical question</th>
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<th>Intervention/ Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
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</thead>
<tbody>
<tr>
<td>● Genetic markers</td>
<td>o PKD1-T, PKD1-NT (hypomorphic vs. fully penetrating), PKD2, others o NOT polymorphisms, SNPs, non-PKD genetic factors.</td>
<td>htTKV (or TKV), any imaging technique ● Other imaging findings (e.g., cyst count, texture) ● Laboratory tests/biomarkers o eGFR (indexed for age) o Urine biomarkers (e.g., crystalluria, urine/plasma urea ratios, tubular biomarkers, albuminuria) o Plasma biomarkers (e.g., glycemia,</td>
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<td>Clinical question</td>
<td>Population</td>
<td>Intervention/Predictor</td>
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<tr>
<td>How do the estimates of htTKV as measured by different imaging techniques compare as predictors of progression of kidney disease?</td>
<td>ADPKD</td>
<td>copeptin, lipid profile, bicarbonate, uric acid)</td>
<td></td>
<td>• Progression of kidney disease</td>
<td>Longitudinal ≥1 yr f/up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Global omics (e.g., proteomics, RNA)</td>
<td></td>
<td>o Change in kidney function (GFR, eGFR, SCr doubling, GFR slope, etc.)</td>
<td>N ≥30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o FGF23</td>
<td></td>
<td>o Change in CKD stage</td>
<td></td>
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<td></td>
<td></td>
<td>o Combinations of tests</td>
<td></td>
<td>o Incident kidney failure</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Urinary tract/cyst infection</td>
<td></td>
<td>• Change in htTKV or TKV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Prevalent diabetes</td>
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<td></td>
<td></td>
<td>• Obesity/BMI</td>
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<td></td>
<td></td>
<td>• Family history of ADPKD (age at kidney failure)</td>
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<td></td>
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<td>Pediatric studies: Any predictor (including BP pattern)</td>
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<td>Clinical question</td>
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<td>Comparator</td>
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</tbody>
</table>
| How do non-TKV measures on imaging compare with hTKV or add as predictors of progression of kidney disease? | ADPKD                    | ● Cyst count            | hTKV       | ● **Progression of kidney disease**  
  ○ Change in kidney function (GFR, eGFR, Scr doubling, GFR slope, etc.)  
  ○ Change in CKD stage  
  ○ Incident kidney failure  
  ● Change in hTKV or TKV | Longitudinal  
  ≥1 yr f/up  
  N ≥30 |

### Chapter 2. Kidney manifestations

#### Hypertension

| What are the comparative effectiveness (benefits) and harms of different BP targets? | ADPKD (with high blood pressure)  
  ○ *A priori* subgroup: known ICA  
  ○ Subgroup by age | BP target | Alternate BP target | ● BP  
  ● CKD progression (by GFR)  
  ● Ruptured ICA  
  ● Death  
  ● Adverse events, serious attributable  
  ● Left ventricular hypertrophy  
  ● PKD progression (by TKV) | Longitudinal  
  ≥1 yr f/up  
  N ≥30 |
| What are the comparative effectiveness (benefits) and harms of different antihypertensive agents? | ADPKD (with HBP)  
  ● *A priori* subgroup  
  ○ Known ICA  
  ○ Diet/fluid intake | Any antihypertensive medication (alone or in combination), including diuretics | Alternative antihypertensive medication (alone or in combination) | ● BP  
  ● CKD progression (by GFR)  
  ● Ruptured ICA  
  ● Death  
  ● AE, serious attributable  
  ● Left ventricular hypertrophy  
  ● PKD progression (by TKV) | RCT (or extension studies of RCTs)  
  ≥1 yr f/up  
  N ≥30 |

For AE:  
Single group  
N ≥30
<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/ Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic kidney pain</strong></td>
<td>ADPKD with kidney or liver cyst infection</td>
<td>PET, 111In WBC, Gallium, MRI, CT, U/S</td>
<td>Alternative imaging test Gold standard (aspiration)</td>
<td>Cyst infection</td>
<td>Comparison with gold standard or alternative test N ≥10</td>
</tr>
<tr>
<td>How accurate are different imaging tests to diagnose kidney or liver cyst infections and how do the different imaging tests compare?</td>
<td>ADPKD with kidney or liver cyst infection</td>
<td>Antibiotic treatment</td>
<td>Different antibiotic (will record specific nature of antibiotic Same treatment with alternate duration of treatment</td>
<td>Cure (infection clearance), Recurrence, Harms</td>
<td>RCT (or extension studies of RCTs) ≥1 yr f/up N ≥10/group For harms: Any longitudinal N ≥30</td>
</tr>
<tr>
<td>How do different antibiotics or duration of antibiotic treatment compare to treat kidney or liver cyst infections?</td>
<td>ADPKD with kidney or liver cyst infection</td>
<td>QoL scale, Pain measure</td>
<td>Alternative QoL or pain measure</td>
<td>Pain, QoL, Progression, Workdays lost, Analgesia dose, type, etc.</td>
<td>Comparative Validation</td>
</tr>
<tr>
<td>What pain or QoL scales have been validated in the ADPKD population?</td>
<td>ADPKD</td>
<td></td>
<td></td>
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<tr>
<td><strong>Renal cell carcinoma (RCC)</strong></td>
<td>ADPKD A priori subgroup: post-transplantation</td>
<td>General population or other people with CKD</td>
<td>Renal cell cancer incidence or prevalence, Type of RCC</td>
<td></td>
<td>Registry (or other generalizable sample)</td>
</tr>
<tr>
<td>Clinical question</td>
<td>Population</td>
<td>Intervention/ Predictor</td>
<td>Comparator</td>
<td>Outcomes*</td>
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<tr>
<td>population or general population?</td>
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<table>
<thead>
<tr>
<th>Chapter 3. Chronic kidney disease management and progression, kidney failure, and kidney replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CKD management and progression</strong></td>
</tr>
</tbody>
</table>

| What are the comparative benefits and harms of peritoneal and hemodialysis in people with ADPKD? | ADPKD with kidney failure (CKD G5D) | PD | HD | • QoL  
• Functional outcomes  
• Psychosocial outcomes  
• Harms: peritonitis  
• Pain  
• Bulk symptoms  
• Death  
• Residual kidney function  
• Tolerability  
• Dialysis efficiency  
• BP control  
• Harms: hernia | Longitudinal  
≥1 month f/up |
| Comparatives  
N ≥10/group |
| For harms:  
Single group of PD (not HD)  
N ≥30 |

| What are the comparative benefits and harms of peritoneal dialysis in people with ADPKD versus people without ADPKD? | People receiving PD | PD in people with ADPKD | PD in people without ADPKD | • QoL  
• Functional outcomes  
• Psychosocial outcomes  
• Harms: peritonitis  
• Pain  
• Bulk symptoms  
• Death  
• Residual kidney function  
• Tolerability  
• Dialysis efficiency  
• BP control  
• Harms: hernia | Longitudinal  
≥1 month f/up |
| Comparatives  
N ≥10/group |
<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/ Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
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</thead>
<tbody>
<tr>
<td><strong>Kidney transplantation</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| What are benefits and harms of nephrectomy for people receiving a kidney transplant or for other indications? | ADPKD | Nephrectomy (any) | No nephrectomy | • Graft loss  
• CKD progression (by GFR)  
• QoL  
• Functional outcomes  
• Psychosocial outcomes  
• Native kidney symptoms [recurring]  
• Native kidney symptoms [acute]  
• Death  
• Surgical complications (CD V, death)  
• Surgical complications (CD III/IV)  
• Surgical complications: transfusions, any  
• Delayed graft function | Any duration  
Comparative  
N ≥50 total  
Exclude studies prior to 2013 |
| What are the comparative benefits and harms of bilateral versus unilateral nephrectomy? | ADPKD | Bilateral nephrectomy | Unilateral nephrectomy | • Graft loss  
• CKD progression (by GFR)  
• QoL  
• Functional outcomes  
• Psychosocial outcomes  
• Native kidney symptoms [recurring]  
• Native kidney symptoms [acute]  
• Death  
• Surgical complications (CD V, death) | Any duration  
Comparative  
N ≥10/group  
(no date exclusions) |
<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/ Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
</tr>
</thead>
</table>
| What are the comparative benefits and harms of different timing of nephrectomy (in relation to time of transplant surgery) for receiving a kidney transplant? | ADPKD receiving kidney transplant and undergoing nephrectomy | ● Pre-transplant nephrectomy  
● At-transplant nephrectomy  
● Post-transplant nephrectomy | Alternate time | • Graft loss  
• CKD progression (by GFR)  
• QoL  
• Functional outcomes  
• Psychosocial outcomes  
• Native kidney symptoms [recurring]  
• Native kidney symptoms [acute]  
• Death  
• Surgical complications (CD V, death)  
• Surgical complications (CD III/IV)  
• Surgical complications: transfusions, any  
• Delayed graft function | Any duration  
Comparative N ≥10/group  
Exclude studies prior to 2013 |
| What are the comparative benefits and harms of different surgical approaches for nephrectomy? | ADPKD undergoing nephrectomy | Laparoscopic nephrectomy | Open nephrectomy | • Graft loss  
• CKD progression (by GFR)  
• QoL  
• Functional outcomes  
• Psychosocial outcomes  
• Native kidney symptoms [recurring] | Any duration  
Comparative N ≥10/group  
Single group N ≥30 |
<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
</tr>
</thead>
</table>
| What are the comparative effects of dietary or lifestyle interventions to slow ADPKD progression? | ADPKD | • Dietary sodium restriction  
• Dietary protein restriction  
• Dietary phosphate restriction  
• Dietary caffeine (xanthin, thein) restriction  
• Dietary acid restriction  
• Dietary bicarbonate/citrate supplementation  
• Caloric restriction (to maintain optimal body weight)  
• Increased water intake | No or alternative dietary intake | • CKD progression (by GFR)  
• QoL  
• Functional outcomes  
• Psychosocial outcomes  
• PKD progression (by TKV)  
• Harm: hyponatremia/metabolic  
• Harm: discontinuation due to AE | Longitudinal  
≥1 yr f/up  
Comparative  
N ≥10/group  
For harms: Single group  
N ≥30 |

Chapter 4. Therapies to delay the progression of kidney disease

| | | | | | |
| Exclude studies prior to 2013 | | | | | |

| | | | | | |
| − Native kidney symptoms [acute]  
− Death  
− Surgical complications (CD V, death)  
− Surgical complications (CD III/IV)  
− Surgical complications: transfusions, any  
− Delayed graft function | | | | | |

| | | | | | |
| Comparative N ≥10/group | | | | | |

| | | | | | |
| For harms: Single group N ≥30 | | | | | |

292
<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/ Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
</tr>
</thead>
</table>
| What are the comparative effects of pharmacologic interventions to slow ADPKD progression? | ADPKD      | ● V2 receptor antagonist  
○ Tolvaptan  
○ Lixivaptan  
● Somatostatin analogues  
○ Octreotide  
○ Lanreotide  
○ Pasireotide  
● Tyrosine kinase inhibitor  
○ Tesevatinib  
● Beta-hydroxy butyrate supplementation  
● Frequent small meals  
● Special diets  
○ Mediterranean  
○ DASH  
○ Vegetarian  
○ Low osmolar  
○ Ketogenic  
○ Intermittent fasting  
○ High fiber (or supplementation)  
● Smoking  
● Exercise  
● Other lifestyle | ● No pharmacologic intervention (including placebo)  
● Alternative pharmacologic intervention | ● CKD progression (by GFR)  
● PKD progression (by TKV)  
● Liver size  
● Death  
● Pain  
● Harms: serious adverse events  
● Harm: liver injury  
● QoL  
● Functional outcomes  
● Psychosocial outcomes  
● Bulk symptoms | RCT (or extension studies of RCTs)  
≥1 yr f/up  
N ≥10/group  
For harms: Any longitudinal  
N ≥30  
(N ≥100 for tolvaptan) |
### Chapter 5. Polycystic liver disease (PLD)

#### What are the comparative effects of dietary or lifestyle interventions to slow liver cyst progression?

<table>
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<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/ Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLD, with or without ADPKD</td>
<td>Dietary caffeine (xanthin, thein) restriction</td>
<td>No or alternative dietary intake or lifestyle intervention</td>
<td>Liver volume, Liver cyst volume, Bulk symptoms, Pain, Harms: serious adverse events, QoL</td>
<td>Longitudinal ≥1 yr f/up</td>
</tr>
<tr>
<td>Clinical question</td>
<td>Population</td>
<td>Intervention/ Predictor</td>
<td>Comparator</td>
<td>Outcomes*</td>
<td>Design</td>
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<tr>
<td>What are the benefits and harms of hormone therapy on polycystic liver disease?</td>
<td>PLD, with or without ADPKD</td>
<td>● Estrogens ○ Estrogen-based oral contraception ○ Other estrogen-based contraception ○ Hormone (replacement) therapy ● Progesterone ● IVF hormonal therapy ● Tamoxifen (and other Selective estrogen receptor modulators)</td>
<td>● No or alternative hormone interventions</td>
<td>● Liver volume ● Liver cyst volume ● Bulk symptoms ● Pain ● Harms: serious adverse events ● QoL ● Functional outcomes ● Psychosocial outcomes ● Harms/AE (diarrhea, bradycardia)</td>
<td>Longitudinal ≥1 yr f/up Comparative or single group N ≥10/group</td>
</tr>
<tr>
<td>Clinical question</td>
<td>Population</td>
<td>Intervention/ Predictor</td>
<td>Comparator</td>
<td>Outcomes*</td>
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<tr>
<td>What harms are associated with different routes of administration of hormone therapy in people with polycystic liver disease?</td>
<td>PLD, with or without ADPKD</td>
<td>● (Risk factors: history of, number of pregnancies)</td>
<td>● Route of delivery (oral, IUD, etc.)</td>
<td>● Liver volume</td>
<td>Longitudinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Estrogens</td>
<td></td>
<td>● Liver cyst volume</td>
<td>≥1 yr f/up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Estrogen-based oral contraception</td>
<td></td>
<td>● Bulk symptoms</td>
<td>Comparative or single group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Other estrogen-based contraception</td>
<td></td>
<td>● Pain</td>
<td>N ≥10/group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Hormone (replacement) therapy</td>
<td></td>
<td>● Harms: serious AEs</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>● Progesterone</td>
<td></td>
<td>● QoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● IVF hormonal therapy</td>
<td></td>
<td>● Functional outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Tamoxifen (and other Selective estrogen receptor modulators)</td>
<td></td>
<td>● Psychosocial outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● (Risk factors: history of, number of pregnancies)</td>
<td></td>
<td>● Harms/AE (diarrhea, bradycardia)</td>
<td></td>
</tr>
<tr>
<td>What are the effects of pharmacologic interventions to slow PLD progression</td>
<td>PLD, with or without ADPKD</td>
<td>● Somatostatin analogues</td>
<td>● No or alternative pharmacologic intervention</td>
<td>● Liver volume</td>
<td>RCT (or extension studies of RCTs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Octreotide</td>
<td></td>
<td>● Liver cyst volume</td>
<td>≥1 yr f/up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Lanreotide</td>
<td></td>
<td>● Bulk symptoms</td>
<td>N ≥10/group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Pasireotide</td>
<td></td>
<td>● Pain</td>
<td>For harms:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Ursodeoxycholic acid</td>
<td></td>
<td>● Harms: serious adverse events</td>
<td>Any longitudinal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● mTOR inhibitors</td>
<td></td>
<td>● QoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>● Functional outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>● Psychosocial outcomes</td>
<td></td>
</tr>
<tr>
<td>Clinical question</td>
<td>Population</td>
<td>Intervention/ Predictor</td>
<td>Comparator</td>
<td>Outcomes*</td>
<td>Design</td>
</tr>
<tr>
<td>-------------------</td>
<td>------------</td>
<td>-------------------------</td>
<td>------------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>What are the effects of invasive procedures or surgery to manage liver or kidney cysts or pain?</td>
<td>ADPKD or PLD, with or without ADPKD</td>
<td>● Cyst aspiration  ● Cyst drainage  ● Cyst sclerosis  ● Embolization (transarterial)  ● Fenestration  ● Liver resection  ● Liver transplantation  ● Nerve blocks  ● Denervation  ● Other invasive pain management</td>
<td>● No or alternative invasive intervention</td>
<td>● Harms/AE (diarrhea, bradycardia)</td>
<td>N ≥30</td>
</tr>
<tr>
<td>What are the benefits and harms of percutaneous drainage to treat liver cyst infections?</td>
<td>PLD, with or without ADPKD, with cyst infection</td>
<td>● Percutaneous drainage</td>
<td>● No drainage</td>
<td>● Cure (infection clearance)  ● Harms</td>
<td>Any duration</td>
</tr>
<tr>
<td>Chapter 6. Intracranial aneurysms (ICA) and other extrarenal manifestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For harms: Single group N ≥30</td>
</tr>
<tr>
<td>What is the prevalence of ICA and the incidence of ruptured ICA in ADPKD?</td>
<td>ADPKD</td>
<td>(None)</td>
<td>(None)</td>
<td>● ICA prevalence  ● Ruptured ICA incidence</td>
<td>Nationally representative population samples (or equivalent)</td>
</tr>
<tr>
<td>Clinical question</td>
<td>Population</td>
<td>Intervention/ Predictor</td>
<td>Comparator</td>
<td>Outcomes*</td>
<td>Design</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>What is the risk of ICA rupture in individuals with ADPKD versus the general population?</td>
<td>General population, either total population or people with no known ICA</td>
<td>ADPKD</td>
<td>No ADPKD</td>
<td>● Ruptured ICA/SAH</td>
<td>Comparative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N ≥30/group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Take temporal effects and imaging techniques into account</td>
</tr>
<tr>
<td>What are the predictors for prevalent ICA or rupture of ICA?</td>
<td>ADPKD</td>
<td>● Any</td>
<td></td>
<td>● ICA</td>
<td>Predictor analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Modifiable risk factors</td>
<td></td>
<td>● ICA rupture</td>
<td>● Comparison of with vs. without risk factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Smoking</td>
<td></td>
<td></td>
<td>N ≥30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o BP control</td>
<td></td>
<td></td>
<td>Take temporal effects and imaging techniques into account</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Nonmodifiable risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Genetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Known aneurysm (or no known aneurysm), for risk of ICA rupture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical question</td>
<td>Population</td>
<td>Intervention/ Predictor</td>
<td>Comparator</td>
<td>Outcomes*</td>
<td>Design</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>What are the benefits and harms of imaging individuals with ADPKD for ICA?</td>
<td>ADPKD</td>
<td>Imaging for ICA</td>
<td>No screening</td>
<td>Death</td>
<td>Longitudinal ≥1 yr f/up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(overlap with imaging)</td>
<td>No comparator</td>
<td>ICA rupture</td>
<td>N ≥30 or N ≥10 with post-imaging intervention (e.g., surgical clipping) (if total N &lt;30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Location and number of previous aneurysms</td>
<td>Alternate imaging strategy</td>
<td>Stroke</td>
<td>Take temporal effects and imaging techniques into account</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Previous treated aneurysms</td>
<td>(including timing of repeat tests)</td>
<td>Intervention complication</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Previous ruptured aneurysms</td>
<td></td>
<td>Psychosocial outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>QoL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Functional outcomes</td>
<td></td>
</tr>
</tbody>
</table>

**Chapter 7. Lifestyle and psychosocial aspects**
No systematic reviews conducted for clinical questions addressed this chapter

**Chapter 8. Pregnancy, reproductive issues**
No systematic reviews conducted for clinical questions addressed this chapter

**Chapter 9. Pediatric issues**
No specific systematic reviews conducted for clinical questions addressed this chapter (addressed by other systematic reviews performed for earlier chapters)

**Chapter 10. Approaches to the management of people with ADPKD**

No systematic reviews conducted for clinical questions addressed this chapter

**Table 16. Clinical questions and systematic review (SR) topics in Population, Intervention, Comparator, Outcomes, and Study Design (PICOD) format.** Bold outcomes are critical; un-bolded outcomes are important. In WBC, indium-labeled white blood cells; ADPKD, autosomal dominant polycystic kidney disease; AMP, adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; anti-miR17, anti-microRNA-17; BMI, body mass index; BP, blood pressure; CD III/IV/V, Clavien-Dindo grade (of complication) III (require intervention)/IV (life-threatening)/V (death); CFTR, cystic fibrosis transmembrane conductance regulator; CKD, chronic kidney disease; CT, computed tomography; DASH, Dietary Approaches to Stop Hypertension; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor-23; GFR, glomerular filtration rate; HD, hemodialysis; HIF-PHI, hypoxia-inducible factor-prolyl hydroxylase inhibitors; htTKV, height-adjusted total kidney volume; IUD, intrauterine device; IVF, *in vitro* fertilization; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; Nrf2, nuclear factor erythroid 2-related factor 2; NT, nontruncating; PD, peritoneal dialysis; PET, positron emission tomography; PLD, polycystic liver disease; PROPKD, Predicting Renal Outcomes in ADPKD; QoL, quality of life; RCT, randomized controlled trial; SAH, subarachnoid hemorrhage; SCr, serum creatinine; SGLT2i: sodium-glucose cotransporter-2 inhibitors; SNP, single nucleotide polymorphisms; T, truncating; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume; U/S, ultrasound; V2, vasopressin-2; yr f/up: year(s) follow-up.

<table>
<thead>
<tr>
<th>Clinical question</th>
<th>Population</th>
<th>Intervention/Predictor</th>
<th>Comparator</th>
<th>Outcomes*</th>
<th>Design</th>
</tr>
</thead>
</table>

No systematic reviews conducted for clinical questions addressed this chapter
Literature search and article selection

The ERT designed comprehensive search strategies for MEDLINE (via PubMed), Embase, the Cochrane Register of Clinical Trials, and the Cochrane Database of Systematic Reviews from inception through October 20, 2022. [This search will be updated during public review.] The search strategies for all databases are provided in Appendix A: Supplementary Tables S1.

The unique titles and abstracts resulting from the searches were screened in duplicate by members of the ERT, using the Abstrackr screening platform (http://abstrackr.cebm.brown.edu/). To establish relevance and consensus among reviewers, the entire team screened and achieved consensus on a series of initial batches of 100 abstracts. Potentially relevant citations were retrieved in full text. These articles were rescreened in duplicate. Disagreement about inclusion was resolved by discussion with the entire team.

The search identified 9481 citations (Figure 58). Of these, 970 were screened in full text, and 224 were extracted and summarized. This included 70 for Chapter 1, 28 for Chapter 2, 33 for Chapter 3, 56 for Chapter 4, 20 for Chapter 5, and 17 for Chapter 6.
Data extraction

Data extraction was performed by one ERT member. Extracted data from each study was reviewed by another ERT member to confirm accuracy. The ERT designed a form to capture data on design, methodology, eligibility criteria, study participant characteristics, interventions, comparators, outcomes, and results of individual studies. Methodology and outcomes were also systematically assessed for risk of bias. Data were extracted into the online repository Systematic Review Data Repository-Plus (SRDR+). The data are available for review at [http://srdrplus.ahrq.gov/](http://srdrplus.ahrq.gov/).

Critical appraisal of studies

Studies were assessed for risk of bias and methodological concerns. We used the Cochrane Risk of Bias tool to evaluate RCTs (that evaluated comparisons of interest). The tool asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases.
For nonrandomized, observational comparative studies (that evaluated comparisons of interest), we used pertinent questions from the Cochrane Risk of Bias tool pertaining to outcome assessor blinding, incomplete outcome data (i.e., missing data and dropouts), and selective reporting. We also used selected questions from the Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool. Specifically, for comparative studies we evaluated whether evaluated cohorts were comparable and whether potential confounders were accounted for.

For all studies, including single group (non-comparative) studies, we determined whether analyses were intention-to-treat (or otherwise included all participants) or were per-protocol (or other incomplete assessment), whether selection of participants into the study was based on participant characteristics observed after the start of intervention, selective reporting, whether there was clear reporting without discrepancies, clear eligibility criteria, adequately described interventions (including dosages and treatment duration), and adequate outcome definition. For studies that reported harms, we assessed whether predefined or standard definitions of adverse events were used. For all studies, we also captured whether there were other potential biases or methodological problems of note. Where methodological issues may have pertained only to some reported outcomes, this was noted.

For each study, assessment of risk of bias was done by one of the reviewers, then confirmed by another, with discrepancies discussed in conference.

**Evidence synthesis and meta-analysis**

Data for the topics with systematic reviews are presented in summary tables and in forest plots where meta-analysis was appropriate.

*Measures of treatment effect* - Dichotomous outcome results were expressed as OR with 95% CI. When continuous scales of measurement were used to assess the effects of treatment the net mean difference (NMD) with 95% CI was used.

*Data synthesis* - We conducted meta-analyses when at least 3 studies (or study groups) of the same design evaluated sufficiently similar interventions in sufficiently similar patients and reported the same outcome. We used our judgment to determine sufficient similarities. We did not exclude meta-analyses solely for statistical heterogeneity (differences across studies in effect size estimates). We conducted restricted maximum likelihood (REML) model meta-analyses of the OR for outcomes in Stata.

*Assessment of heterogeneity* – Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes and of risk ratios, and $\chi^2$ tests. A $P < 0.05$ was used to denote statistical heterogeneity, with an $I^2$ calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.
Grading the certainty of the evidence and the strength of a guideline recommendation

Evidence profiles

Evidence profiles were developed to include a description of the population and the intervention and comparator. In addition, the evidence profiles include risk of bias rating and results from the data synthesis. The grading of the certainty of the evidence for each critical and important outcome is also provided in these tables. The SoF tables are available in the Data Supplement Appendixes C and D.

GRADING the certainty of the evidence for each outcome across studies

The overall certainty of the evidence related to each critical and important outcome was assessed using the GRADE approach (Table 17), which assesses the certainty of the evidence for each outcome. For each outcome, the potential grade for the certainty of evidence for each intervention-outcome pair started at “high” but was then lowered if there were serious limitations to the methodological certainty of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence (including limited applicability of the findings to the population of interest), if the outcome measure estimates were imprecise or based on sparse studies, or if there was thought to be a high likelihood of reporting bias. The final grade for the certainty of the evidence for an outcome could be high, moderate, low, or very low (Table 17).

The overall certainty of evidence - The overall certainty of the evidence was based on the certainty of evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall certainty of the evidence was graded A, B, C, or D (Table 18).
<table>
<thead>
<tr>
<th>Study design</th>
<th>Starting grade for the certainty of the evidence</th>
<th>Step 2—Lower the grade</th>
<th>Step 3—Raise the grade for observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>High</td>
<td>Study limitations:</td>
<td>Strength of association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−1, serious</td>
<td>+1, large effect size (e.g., &lt;0.5 or &gt;2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2, very serious</td>
<td>+2, very large effect size (e.g., &lt;0.2 or &gt;5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Inconsistency:</td>
<td>1, serious</td>
<td>Evidence of a dose–response gradient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2, very serious</td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>Low</td>
<td>Indirectness:</td>
<td>All plausible confounding would reduce the demonstrated effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>−1, serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2, very serious</td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>Imprecision:</td>
<td>1, serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2, very serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Publication bias:</td>
<td>1, serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>−2, very serious</td>
<td></td>
</tr>
</tbody>
</table>

Table 17. GRADE system for grading certainty of evidence. GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized controlled trial.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Certainty of evidence</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are confident that the true effect is close to the estimate of the effect.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>The estimate of effect is very uncertain, and often it will be far from the true effect.</td>
</tr>
</tbody>
</table>

Table 18. Classification for certainty of the evidence.

Grading the strength of the recommendations

The strength of a recommendation is graded as strong or weak (Table 19). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and other considerations (Table 20).
Grade | Implications
---|---
**Level 1, “We recommend”** | Patients: Most people in your situation would want the recommended course of action, and only a small proportion would not. | Clinicians: Most patients should receive the recommended course of action. | Policy: The recommendation can be evaluated as a candidate for developing a policy or a performance measure. |
**Level 2, “We suggest”** | Patients: The majority of people in your situation would want the recommended course of action, but many would not. | Clinicians: Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences. | Policy: The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined. |

**Table 19. KDIGO nomenclature and description for grading recommendations.** KDIGO, Kidney Disease: Improving Global Outcomes.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance of benefits and harms</td>
<td>The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is provided.</td>
</tr>
<tr>
<td>Certainty of evidence</td>
<td>The higher the certainty of the evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low certainty of the evidence will warrant a strong recommendation.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.</td>
</tr>
<tr>
<td>Resource use and costs</td>
<td>The higher the cost of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.</td>
</tr>
</tbody>
</table>

**Table 20. Determinants of the strength of recommendation.**

**Balance of benefits and harms** - The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

**Patient values and preferences** - The Work Group included 3 people living with ADPKD. These members’ unique perspectives and lived experience, in addition to the Work Group’s understanding of patient preferences and priorities, also informed decisions about the strength of the
recommendations. A systematic review of qualitative studies on patient priorities and preferences was not undertaken for this guideline.

**Resource use and costs** - Healthcare and non-healthcare resources, including all inputs in the treatment management pathway, were considered in grading the strength of a recommendation.\(^{468}\) The following resources were considered: direct healthcare costs, non-healthcare resources (such as transportation and social services), informal caregiver resources (e.g., time of family and caregivers), and changes in productivity. No formal economic evaluations, including cost-effectiveness analysis, were conducted.

**Developing the recommendations**

The guideline statements were developed by the Work Group Co-Chairs and Work Group members. Recommendations were developed during in-person meetings (Berlin, Germany, June 2022 and Paris, France, October 2022) and by e-mail communication. The final draft was sent for external public review, and reviewers provided feedback for consideration by the Work Group. Based on feedback, the guideline was further revised by the Work Group, as appropriate. All Work Group members provided input on initial and final drafts of the guideline statements and guideline text and approved the final version of the guideline. The ERT also provided a descriptive summary of the assessment of the certainty of evidence in support of the graded recommendations.

**Practice points**

In addition to graded recommendations, KDIGO guidelines now include practice points to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care and supplement recommendations for which a formal evidence review was conducted. Practice points represent the expert judgment of the guideline Work Group, but they may be based on limited evidence. Practice points are sometimes formatted as a table, a figure, or an algorithm, to make them easier to use in clinical practice.

**Format for guideline recommendations and practice points**

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1, “we recommend” or Level 2, “we suggest”) and the certainty of the evidence (A, B, C, D). The recommendation statements are followed by key information (Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation) and Rationale. Each recommendation is linked to relevant SoF tables. As mentioned, practice points may be presented in a variety of formats. In most cases, an underlying rationale or graphic supports each practice point. Practice points specifically addressing the implementation of a graded recommendation may be presented with the recommendation statement.
Limitations of the guideline development process

Although the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE, Embase, and Cochrane databases were searched, but other specialty or regional databases were not. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. Recent conference abstracts were screened from several professional society meetings, but older conference abstracts and other conference meetings were not specifically screened. However, any important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

The ERT did not systematically review all topics including, as noted in Table 16, lifestyle and psychosocial interventions (other than selected dietary interventions), interventions specifically related to pregnancy and reproduction, and general approaches to management of people with ADPKD; and specific topics including management of nephrolithiasis, kidney cyst hemorrhage, and most nonrenal manifestations. For certain topics, we applied restrictive eligibility criteria, such as higher minimum sample sizes, restriction to more recent studies, and exclusion of conference abstracts (for multivariable risk factor analyses). We did not review qualitative research studies (e.g., focus groups) to inform determinations about values and preferences, or cost-effectiveness analyses to inform determinations about resource use or costs.
Olivier Devuyst, MD, PhD (Work Group Co-Chair)
Advisory Board: Otsuka* and Galapagos*
Consultancy: Otsuka*, Sanofi-Genzyme*, and Vertex*

Vicente E. Torres, MD, PhD (Work Group Co-Chair)
Consultancy: Janssen*, Mironid*, Palladio Biosciences*, Reata*, Sanofi-Genzyme*, Tribune*, and Vertex*

Curie Ahn, MD, PhD
Reported no relevant financial relationships

Thijs R.M. Barten, MD, PhD
Reported no relevant financial relationships

Godela Brosnahan, MD
Reported no relevant financial relationships

Melissa Cadnapaphornchai, MD
Consultancy: Otsuka

Arlene B. Chapman, MD
Consultancy: Otsuka, Reata, and Sanofi-Genzyme
Grants/Grants Pending: NIDDK*
Speaker Bureaus: Otsuka
Development of Educational Presentations: Otsuka and Sanofi

Emilie Cornec-Le Gall, MD, PhD
Reported no relevant financial relationships

Joost P.H. Drenth, MD, PhD
Grants/Grants Pending: Gilead*
Ron T. Gansevoort, MD, PhD
Consultancy: AstraZeneca*, Bayer Healthcare*, Galapagos*, Otsuka*, and Sanofi-Genzyme*
Other: Owner of the OMPD status for lanreotide*

Peter C. Harris, PhD
Consultancy: BridgeBio*, Janssen*, Maze Therapeutics*, Mitobridge*, Otsuka*, Regulus*, and Vertex Pharmaceuticals*
Grants/Grants Pending: Espervia*, Janssen*, Jemincare*, Merck*, and Otsuka*

Tess Harris, MA
Educational unrestricted grants: GSK UK*, Palladio Biosciences*, and Sanofi-Genzyme*
Consultancy: Palladio Biosciences*
Hospitality: Palladio Biosciences

Shigeo Horie, MD, PhD
Board Member: Kyowa-Kirin, Sanofi, and Welsia
Grants / Grants Pending: Otsuka*

Max C. Liebau, MD
Advisory Board Member: Otsuka*

Michele Liew
Reported no relevant financial relationships

Andrew J. Mallett, MBBS, MMed, PhD
Grants/Grants Pending: MRFF*, PKD Australia*, and Sanofi-Genzyme*
Site PI: Dicerna*, Reata*, and Sanofi-Genzyme*
Travel Expenses: Otsuka

Changlin Mei, MD
Reported no relevant financial relationships

Djalila Mekahli, MD, PhD
Board Member: Otsuka* and Sanofi-Genzyme*
Consultancy: Otsuka*
Grants/Grants Pending: Astellas*, Galapagos*, and Sanofi-Genzyme*
Dwight Odland
Stock/Stock Options: Santa Barbara Nutrients

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Advisory Board: Mironid*
Steering Committee: Sanofi-Genzyme* and Palladio*
Consultancy: Galapagos* and Janssen*

Luiz F. Onuchic, MD, PhD
Steering Committee: Palladiobio*
Consultancy: Otsuka*

York P-C Pei, MSc, MD, FRCPC
Advisory board: Maze Therapeutic, Otsuka, Reata, and Sanofi

Ronald D. Perrone, MD
Steering Committee: Palladiobio* and Sanofi-Genzyme*
Consultancy: Caraway, Janssen*, Navitor, Otsuka*, and Sanofi-Genzyme
Grants/Grants Pending: Kadmon*, Reata*, Palladiobio*, and Sanofi-Genzyme*
Development of Educational Presentations: Haymarket Medical
Other: UpToDate

Gopala K. Rangan, MD
Consultancy: Sanofi-Genzyme
Grants/Grants Pending: Danone Research*, National Health and Medical Research Council of Australia*, Otsuka Australia*, PKD Australia*
Speakers Bureaus: PKD Australia*
Travel Expenses: Otsuka

Brian Rayner, MBChB, FCP, MMED, PhD
Advisory Board: AstraZeneca, Sanofi-Genzyme, and Servier
Speakers Bureaus: AstraZeneca, Boehringer-Ingelheim, Cipla, Novartis, Sanofi-Genzyme, and Servier

Roser Torra, MD, PhD
Consultancy: Alnylam, Amicus, Chiesi, and Ipsen
Speakers Bureaus: Alnylam, Amicus, Chiesi, Kyowa-Kirin, Otsuka, Sanofi-Genzyme, and Takeda
Development of Educational Presentations: Alnylam, Amicus, Otsuka, Sanofi-Genzyme, and Takeda

*Monies paid to institution
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Patient-reported outcome measures (PROMs) are standardized, validated methods or tools used to measure patient-reported outcomes (PROs). A PRO is “a measurement based on a report that comes directly from the patient about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient’s response”.

PROMs are validated surveys administered by various means (e.g., paper, online), and the patient may be asked to complete these prior, during, or after a clinic appointment, or after treatment/interventions. PROMs can be collected at several points of time and can be useful for monitoring progress, helping communication between the patient and the healthcare team, encouraging patient engagement, and helping to improve overall care. Typically, PROMs consist of rating scales or event counts.

There are 3 types of PROMs that can be used in the care of patients with ADPKD:
- Generic - used to survey patients with any condition with a focus on general well-being, mental health, and/or QoL,
- CKD-specific – focusing on outcomes that matter most to any CKD patient,
- ADPKD-specific – focusing on key symptoms and manifestations of ADPKD.

The growth of PROMs usage in audit, clinical management (especially linked to cost effectiveness and healthcare efficiencies), and clinical trials has resulted in many tools being developed. Some have been developed for single studies or for single center use. Most have not been validated. Results may not be comparable and there is a risk of clinicians and patients being overwhelmed with too many and differing surveys.

Despite the growth in new tools, a few generic PROMs are commonly used to measure health status, symptoms, functioning, satisfaction, or health-related quality-of-life (HRQOL) such as the 36-Item Short Form Survey (SF-36).

Below is a summary of suggested PROMs appropriate for patients with ADPKD. Caveats about many of the PROMs are discussed in the Note column.
<table>
<thead>
<tr>
<th>PRO</th>
<th>PROM</th>
<th>Note</th>
<th>Link (usage licenses may be needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADPKD-specific</strong></td>
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<tr>
<td>ADPKD Genetic Psychosocial Risk Instrument</td>
<td>ADPKD-GPRI</td>
<td>Single center validated GPRI modified to specifically explore the psychosocial impact of coping with a diagnosis of ADPKD</td>
<td><a href="https://academic.oup.com/ndt/article/31/7/1130/1751693">https://academic.oup.com/ndt/article/31/7/1130/1751693</a></td>
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<tr>
<td>Polycystic Liver Disease Symptom Frequency and Discomfort</td>
<td>PLD-Q</td>
<td>Has been accepted within the process of the FDA COA Qualification Program</td>
<td><a href="https://eprovide.mapi-trust.org/instruments/polycystic-liver-disease-questionnaire">https://eprovide.mapi-trust.org/instruments/polycystic-liver-disease-questionnaire</a></td>
</tr>
<tr>
<td>Polycystic Liver Disease Complaint-specific Assessment</td>
<td>POLCA</td>
<td>Self-report instrument to capture the presence and severity of disease specific complaints for PCLD.</td>
<td>No information</td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td></td>
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<tr>
<td>Generic QOL</td>
<td>WHOQOL-100 or WHOQOL-BREF</td>
<td>Most PROMs used in healthcare only measure HRQoL and not QoL, which is defined by the WHO as an “individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.” The</td>
<td><a href="https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03">https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03</a></td>
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<tr>
<td><strong>PRO</strong></td>
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<td>WHO QOL lists 6 domains with 24 facets which cover: physical, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs.</td>
<td></td>
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</tr>
<tr>
<td>Generic CKD HRQOL – ICHOM Set of Patient-Centered Outcome Measures for Chronic Kidney Disease**</td>
<td>SF-36</td>
<td>The ICHOM developed an “International Standard Set of Value-Based Outcome Measures for Patients with CKD” which includes PROMs. The working group prioritized 6 patient-reported outcome domains for HRQoL: general HRQoL, pain, fatigue, physical function, depression, and daily activity. Three tools were recommended as shown in left column.</td>
<td><a href="https://www.qualitymetric.com/health-surveys/the-sf-36v2-health-survey/">https://www.qualitymetric.com/health-surveys/the-sf-36v2-health-survey/</a> <a href="https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html">https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html</a> <a href="https://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures">https://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures</a></td>
</tr>
<tr>
<td>Anxiety</td>
<td>GAD-7</td>
<td>Widely used to identify probable cases of generalized anxiety disorder and assess symptom severity in generalized anxiety disorder.</td>
<td><a href="https://eprovide.mapi-trust.org/instruments/generalized-anxiety-disorder-7">https://eprovide.mapi-trust.org/instruments/generalized-anxiety-disorder-7</a></td>
</tr>
<tr>
<td>Depression severity</td>
<td>BDI®-II</td>
<td>Widely used to measure the severity of depression in adults and adolescents</td>
<td><a href="https://eprovide.mapi-trust.org/instruments/beck-depression-inventory-r-second-edition">https://eprovide.mapi-trust.org/instruments/beck-depression-inventory-r-second-edition</a></td>
</tr>
<tr>
<td>Mental health</td>
<td>PHQ</td>
<td>To diagnose mental disorders in primary care (various versions)</td>
<td><a href="https://eprovide.mapi-trust.org/instruments/patient-health-questionnaire">https://eprovide.mapi-trust.org/instruments/patient-health-questionnaire</a></td>
</tr>
<tr>
<td>Pain</td>
<td>BPI</td>
<td>Widely used to assess the severity of pain and the impact of pain on daily functions</td>
<td><a href="https://eprovide.mapi-trust.org/instruments/brief-pain-inventory">https://eprovide.mapi-trust.org/instruments/brief-pain-inventory</a></td>
</tr>
</tbody>
</table>

**Pediatric**

<p>| Pediatric Quality of Life Survey | PedSQL | The PedSQL is a brief measure of health-related QoL in children and young people. The measure can be completed by parents (the Proxy Report) as well as children and young people (the Self-Report). | <a href="https://www.corc.uk.net/outcome-experience-measures/pediatric-quality-of-life-pedsql">https://www.corc.uk.net/outcome-experience-measures/pediatric-quality-of-life-pedsql</a> |
| Pediatric HRQOL | PROMIS® Pediatric | No information | <a href="https://www.niams.nih.gov/grants-funding/niams-supported-research-">https://www.niams.nih.gov/grants-funding/niams-supported-research-</a> |</p>
<table>
<thead>
<tr>
<th>PRO</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Instrument Banks</td>
<td></td>
<td></td>
<td><a href="https://eprovide.mapi-trust.org/advanced-search">programs/pediatric-patient-reported-outcomes-chronic</a></td>
</tr>
</tbody>
</table>

**Appendix Table 1. List of suggested PROMs appropriate for patients with ADPKD.** ADPKD, autosomal dominant polycystic kidney disease; ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease Impact Scale; ADPKD-PDS, Autosomal Dominant Polycystic Kidney Disease Pain and Discomfort Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease Urinary Impact Scale; APAT, ADPKD-specific pain assessment tool; BDI-II, Beck Depression Inventory-Second Edition; BPI, Brief Pain Inventory; CKD, chronic kidney disease; COA, clinical outcome assessment; FDA, U.S. Food and Drug Administration; GAD-7, Generalized Anxiety Disorder–7; GPRI, genetic psychosocial risk instrument; HRQOL, health-related quality of life; ICHOM, International Consortium for Health Outcomes Measurement; KTQ-25, Kidney Transplant Questionnaire-25-items; PedsQL, Pediatric Quality of Life Inventory; PHQ, Patient Health Questionnaire; PRO, patient-reported outcome; PROM, patient-reported outcome measure; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; SF-36, 36-Item Short Form Survey; WHO, World Health Organization

**ADDITIONAL PROMS:**
[https://eprovide.mapi-trust.org/advanced-search](https://eprovide.mapi-trust.org/advanced-search)

**IMPLEMENTATION:**