OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

SUPPLEMENT TO

kidney® INTERNATIONAL

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES

KDIGO®

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

VOLUME 107 | ISSUE 2S | FEBRUARY 2025

www.kidney-international.org

KDIGO 2025 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION, MANAGEMENT, AND TREATMENT OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

VOL 107 | ISSUE 2S | FEBRUARY 2025

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

This article is published as part of a supplement sponsored by Kidney Disease: Improving Global Outcomes (KDIGO).

TABLES

FIGURES

SUPPLEMENTARY MATERIAL

Supplementary material is available online at www.kidney-international.org.

KDIGO EXECUTIVE COMMITTEE

Garabed Eknoyan, MD
Norbert Lameire, MD, PhD
Founding KDIGO Co-Chairs

Wolfgang C. Winkelmayer, MD, MPH, ScD
Immediate Past Co-Chair

Michel Jadoul, MD
KDIGO Co-Chair

Morgan E. Grams, MD, PhD, MHS
KDIGO Co-Chair

Gloria E. Ashuntantang, MD
Sunita Bavanandan, MBBS
Irene de Lourdes Noronha, MD, PhD
Michelle R. Denburg, MD, MSCE
Joachim H. Ix, MD, MAS
Vivekanand Jha, MD, DM, FRCP, FAMS
Holly Kramer, MD, MPH
Adrian Liew, MD, MBBS, MRCP, FAMS, FASN, FRCP, MClinEpid
Reem A. Mustafa, MD, PhD, MPH
Michelle M. O'Shaughnessy, MB, BCh, BAO, MS, MD
Patrick Rossignol, MD, PhD
Paul E. Stevens, MB, FRCP
Rita S. Suri, MD, MSc
Irma Tchokhonelidze, MD
Marc G. Vervloet, MD, PhD, FERA
Wolfgang C. Winkelmayer, MD, MPH, ScD
Motoko Yanagita, MD, PhD

KDIGO Staff

Danielle Green, Chief Executive Officer
Melissa Thompson, Chief Operating Officer
Michael Cheung, Chief Scientific Officer
Amy Earley, Guideline Development Director
Jennifer King, Director of Medical Writing
Tanya Green, Education Director
Coral Cyzewski, Program Director
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 graded as **A**, **B**, **C**, or **D**.

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	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.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

Practice points are consensus-based statements representing the expert judgment of the Work Group and are not graded. They are issued when a clinical question did not have a systematic review performed, to help readers implement the guidance from graded recommendations (e.g., frequency of monitoring, provision of standard care [such as regular clinic visits], referral to specialist care, etc.), or for issuing "good practice statements" when the alternative is considered to be absurd. Users should consider the practice point as expert guidance and use it as they see fit to inform the care of patients. Although these statements are developed based on a different methodology, they should not be seen as less important or a downgrade from graded recommendations.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

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

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers 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

	Conventional unit	Conversion factor	SI unit
ACR	mg/g	0.113	mg/mmol
Creatinine	mg/dl	88.4	μmol/l
LDL cholesterol	mg/dl	0.0259	mmol/l
PCR	mg/dl	0.113	mg/mmol
Sirolimus	ng/ml	1.1	nmol/l

ACR, albumin-to-creatinine ratio; LDL, low-density lipoprotein; PCR, protein-creatinine ratio; SI, International System of Units.
Note: Conventional unit × conversion factor = SI unit.

EQUIVALENT ALBUMINURIA CATEGORIES IN CKD

		ACR (approximate equivalent)		
Category	AER (mg/24 h)	(mg/mmol)	(mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased[a]
A3	>300	>30	>300	Severely increased

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; CKD, chronic kidney disease.
[a]Relative to young adult level.

Abbreviations and acronyms

^{18}F-FDG PET-CT	^{18}F-fluorodeoxyglucose integrated with positron emission tomography/computed tomography
ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin-converting enzyme inhibitor(s)
ACMG	American College of Medical Genetics and Genomics
ADPKD	autosomal dominant polycystic kidney disease
ADPLD	autosomal dominant polycystic liver disease
ADTKD	autosomal dominant tubulointerstitial kidney disease
AKI	acute kidney injury
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
ARPKD	autosomal recessive polycystic kidney disease
AST	aspartate aminotransferase
AVP	arginine vasopressin
BMI	body mass index
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
CRISP	Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease
CRP	C-reactive protein
CT	computed tomography
CTA	computed tomography angiography
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
EO	early onset
ERA	European Renal Association
ERKNET	European Rare Kidney Disease Reference Network
ERT	Evidence Review Team
EU	European Union
GFR	glomerular filtration rate
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HALT-PKD	HALT Progression of PKD
HBPM	home blood pressure monitoring
HD	hemodialysis
HR	hazard ratio
htLCV	height-adjusted liver cyst volume
htTLV	height-adjusted total liver volume
htTKV	height-adjusted total kidney volume
ICA	intracranial aneurysm
IUD	intrauterine device
IVF	*in vitro* fertilization
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	kidney replacement therapy
LAR	long-acting release
LFT	liver function test
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
MIC	Mayo Imaging Classification
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
(t)NGS	targeted next-generation sequencing
NIH	National Institutes of Health
NPV	negative predictive value
NSAIDS	nonsteroidal anti-inflammatory drugs
NT	nontruncating
OR	odds ratio
PD	peritoneal dialysis
PGT	preimplantation genetic testing
PHASES	Population, Height, Age, Size of aneurysm, Earlier subarachnoid hemorrhage from another aneurysm, Site of aneurysm
PICOD	population, intervention, comparator, outcomes, study design
PKD	polycystic kidney disease
PLD	polycystic liver disease
PLD-Q	Polycystic Liver Disease Questionnaire
PlGF	placental growth factor
POLCA	Polycystic Liver Disease Complaint-specific Assessment
PPV	positive predictive value
PREVENT-ADPKD	Prevent Kidney Failure due to Autosomal Dominant Polycystic Kidney Disease
PROPKD	Predicting Renal Outcomes in PKD
QoL	quality of life
RAS(i)	renin-angiotensin system (inhibitor)
RCC	renal cell carcinoma
RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
REPRISE	Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD
RR	relative risk
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
SCr	serum creatinine
sFlt-1	soluble fms-like tyrosine kinase-1

SGLT2i	sodium-glucose cotransporter-2 inhibitor(s)
SONG-PKD	Standardized Outcomes in Nephrology-Polycystic Kidney Disease
T	truncating
TAA	thoracic aortic aneurysm
TEMPO 3:4	Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes
TKV	total kidney volume
TLV	total liver volume
TMP-SMX	trimethoprim-sulfamethoxazole
UK	United Kingdom
ULN	upper limit of normal
U.S.	United States
UTI	urinary tract infection
V_2	vasopressin-2
VEO	very early onset
VUS	variant of uncertain significance
WES	whole exome sequencing
WGS	whole genome sequencing
WHO	World Health Organization

Notice

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in October 2023. 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. Healthcare 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.

Foreword

Kidney International (2025) **107** (Suppl 2S), S1–S239 https://doi.org/10.1016/j.kint.2024.07.009

Comprehensive, evidence-based guidelines for managing disease are critical as we navigate the complexities of global health. The publication of a new guideline signifies an important landmark: the accumulation of sufficient high-certainty evidence to provide a clear-cut road map of diagnosis and care. It heralds a new opportunity to implement best practices across populations and countries, with the goal of decreasing variability in practice patterns and improving quality of life and clinical outcomes. The Kidney Disease: Improving Global Outcomes (KDIGO) 2025 Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)—the most common monogenic kidney disease worldwide—is thus a celebration of scientific progress and a concerted effort to provide a comprehensive resource for healthcare providers. This guideline presents a new nomenclature, thoroughly discusses current diagnostic (including imaging and genetic testing) and therapeutic options (including drug therapy and lifestyle), reports on specific issues related to women and children, and emphasizes the importance of multidisciplinary care.

Established in 2003, KDIGO is committed to publishing the highest quality guidelines through a process marked by rigor and transparency. Work Group members are selected for their expertise and carefully screened for conflicts of interest. Patients are always included as key stakeholders. The Work Group composition is carefully balanced to reflect the diversity in geography and expertise that helps KDIGO in its global mission, with purposeful inclusion across genders. The Scope of Work is developed and made public for comments. After public review, the literature is thoroughly evaluated by an independent, external Evidence Review Team, who help guide the appraisal of the evidence. The Work Group then drafts a set of recommendations (backed by a systematic review) and practice points (not backed by a systematic review) that is again made available for public review. All received comments are reviewed, and the guideline is revised appropriately, with the aim of achieving a guideline that is not only scientifically sound but also practical and applicable to a wide range of contexts.

This guideline on ADPKD is the first of its kind by KDIGO. We are immensely grateful to the Work Group Co-Chairs—Drs. Olivier Devuyst, MD, PhD, and Vicente Torres, MD, PhD—for the incredible time and effort they devoted to this resource. We thank the Work Group members, who volunteered countless hours in the development of recommendations and practice points, and the Evidence Review Team, led by Ethan Balk, MD, MPH and Craig Gordon, MD, MS. We thank the Methods Committee, established by Dr. Marcello Tonelli, MD, SM, MSc, FRCPC, and currently chaired by Dr. Reem A. Mustafa, MD, PhD, MPH, who served as Methods liaison for this guideline, for ensuring the rigor and structure of the processes. Finally, we thank the KDIGO staff, particularly Amy Earley, Melissa Thompson, and Michael Cheung, who shepherded all aspects of guideline development processes with unfailing skill and patience.

Most significantly, we would like to remember one of the ADPKD Guideline Work Group members, Tess Harris, who passed away March 1, 2024. Tess was a longtime volunteer with KDIGO, and her tireless activism, optimism, and unfailing kindness were an inspiration to all those who were privileged to know her. She had a profound impact on the PKD community, and we view this guideline as part of her enormous legacy.

Morgan E. Grams, MD, PhD, MHS
Michel Jadoul, MD
KDIGO Co-Chairs

Dedication: Tess (Teresa) Harris, MA, FCIM (1956–2024): dedicated patient advocate in the fight against polycystic kidney disease (PKD)

Tess (Teresa) Harris was born in the village of Spinkhill, Derbyshire, United Kingdom (UK), the third of 6 children from a close-knit and loving family. Her family describes her as having had an independent streak from an early age, along with a strong sense of adventure, curiosity, a love of horses, and a great love of science. She was, however, ready to leave home from a young age. Having completed her secondary schooling at Notre Dame in Sheffield, she enrolled in a course to study nuclear physics, at the University of Liverpool, before deciding that both the course and her (predominantly male) peers were not to her liking. As she was looking for an alternative career, her mother suggested she enroll in the local secretarial and technical college, which she did, and where she excelled immediately. This route led ultimately to a very successful career in business and marketing consultancy. Tess went on to become a serial entrepreneur and started several businesses, which she later sold. Having served as President of the Chartered Institute of Marketing, she was awarded a fellowship by the institute, and also the Freedom of the City of London. She later completed an MA in Marketing.

Tess joined the PKD Charity as a volunteer in 2004, and she quickly rose to become a trustee, before becoming Chief Executive Officer in 2012. With energy, creativity, and dedication, she led the charity into a new phase of engagement, with several initiatives to support people with PKD and improve the standards of patient care across the UK. These initiatives included establishment of the following: a year-round phone helpline; regular information and support days across the country (50 held to date); accredited patient information online and offline; local patient-support groups; and finally, the first PKD app. Tess served as the first patient chair of a Clinical Study Group (PKD) for the UK Kidney Association. She initiated the PKD research priority–setting partnership with the James Lind Alliance, which established the top 10 topics for PKD research within the UK. This achievement was followed swiftly by the launch of a new, joint, grant-partnership scheme between the PKD Charity and Kidney Research UK, designed to fund vital ground-breaking research in autosomal dominant (AD)PKD. She was instrumental in making the PKD Charity a key partner in several major recent research initiatives in the UK and Europe (i.e., Implementation of Metformin Therapy to Ease Decline of Kidney Function in Polycystic Kidney Disease [IMPEDE-PKD]; Autosomal Dominant Polycystic Kidney Disease, or ADPKD, Advancement of Disease-modifying therapies through a European consortium [ADVANTAGE]; the Renal Ciliopathies National Network [CILIAREN]; the European research consortium on Therapies for Renal Ciliopathies [TheRACiL]; and the European Rare Kidney Disease Reference Network [ERKNet]). Her opinion as a patient expert was sought by regulatory bodies, such as the European Medicines Agency (EMA) and the National Institute for Health and Care Excellence (NICE).

Beyond her work in the UK, she cochaired the European ADPKD Forum (EAF), which established the first multidisciplinary guidance for patient care across the European Union and proposed a lifelong care pathway from diagnosis (https://www.pkdinternational.org/adpkd-route-map). She served as President of PKD International from 2011, an association she started with the goals of linking PKD patient groups globally and championing international partnerships to advance research and patient-support initiatives. Later, she served as President of the Federation of European Patient Groups Affected by Rare and/or Genetic Kidney Diseases (FEDERG), the major kidney-patient association in Europe. She initiated the Ciliopathy Alliance in 2010, to highlight the cause of patients with rarer forms of PKD, and started a biannual scientific meeting that has continued to meet since 2012. Tess was a strong supporter of the pediatric nephrology

community, championing the voice of children who have or are at risk for developing ADPKD, and she sought to improve their care through the establishment of the Rare Diseases Registry Program (RaDAR) and A Global Online Platform on the Management of Children with ADPKD (ADPedKD) childhood registries. She contributed to the impactful work of the Standardized Outcomes in Nephrology-Polycystic Kidney Disease (SONG-PKD) and the PKD Outcomes Consortium (PKDOC), and coauthored 24 papers on ADPKD, with a particular focus on patient outcomes, standards, and guidelines (https://pubmed.ncbi.nlm.nih.gov/?term=tess%20harris%20pkd&sort=date). Finally, she played a key role in the development of the first-ever KDIGO ADPKD guideline, bringing to bear not only her personal insights as a patient, but also a wealth of experience from her interactions with patients from across the world.

Beyond her professional accomplishments, Tess will be remembered by friends and charity supporters for her warmth, empathy, and boundless optimism. Her infectious smile and unwavering energy brought solace and support to all who crossed her path, especially those for whom she was the first point of contact with the charity after they had received a PKD diagnosis, often through the phone-in helpline.

Tess was completely dedicated to the cause of improving the lives of people with PKD. She often would share her personal experience with PKD openly, as well as the impact of PKD on her family publicly. Despite a life of many accomplishments, she retained a touching humility, fierce loyalty to her family and close friends, an earthy wisdom, and a cheeky sense of humor. Even as her health deteriorated, she was working on the final drafts of the KDIGO ADPKD guideline. As a group, we dedicate this guideline to the memory of the life and work of this remarkable colleague and treasured friend. Tess will be missed greatly by her family, friends, colleagues, and many in the worldwide PKD community.

Albert Ong, Djalila Mekahli, Dwight Odland
On behalf of the KDIGO ADPKD Guideline Working Group

ACKNOWLEDGMENTS

We thank Bernadette McKenzie and Fiona Charlesworth for sharing their stories about Tess and Jane Pugh (PKD Charity), for this biographical information.

SELECTED READING

1. Gittus M, Harris T, Ong AC. Patient perspectives on ADPKD. *Adv Kidney Dis Health.* 2023;30:294–302.
2. Harris T, Bridges HR, Brown WD, et al. Research priorities for autosomal dominant polycystic kidney disease: a UK priority setting partnership. *BMJ Open.* 2022;12: e055780.
3. Oberdhan D, Palsgrove AC, Cole JC, Harris T. Caregiver burden of autosomal dominant polycystic kidney disease: a qualitative study. *Kidney Med.* 2022;5:100587.
4. Harris T. Is it ethical to test apparently "healthy" children for autosomal dominant polycystic kidney disease and risk medicalizing thousands? *Front Pediatr.* 2018;5:291.
5. EAF Co-Chairs; Harris T, Sandford R, et al. European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care: European ADPKD Forum and Multispecialist Roundtable participants. *Nephrol Dial Transplant.* 2018;33:563–573.
6. Youssouf S, Harris T, O'Donoghue D. More than a kidney disease: a patient-centred approach to improving care in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* 2015;30:693–695.

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, Minnesota, USA

WORK GROUP

Curie Ahn, MD, PhD
Seoul National University
Seoul, Republic of Korea

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

Godela Brosnahan, MD, PhD, FASN
University of Colorado
Aurora, Colorado, USA

Melissa A. Cadnapaphornchai, MD
Children's Hospital of Philadelphia
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania, USA

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

Emilie Cornec-Le Gall, MD, PhD, FERA
University Hospital of Brest
Brest, France

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

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

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

Tess Harris, MA, FCIM
Polycystic Kidney Disease Charity UK
London, UK

Shigeo Horie, MD, PhD
Juntendo University
Tokyo, Japan

Max C. Liebau, MD
University Hospital Cologne
Cologne, Germany

Michele Liew, MBBS, FRACP, PGDipAvMed
Patient partner
Hong Kong, China

Andrew J. Mallett, MBBS, MMed, PhD, FRCP, FASN, FRACP
Townsville University Hospital
Townsville, Queensland, Australia

Changlin Mei, MD
Changzheng Hospital
Shanghai, China

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

Dwight Odland
PKD Foundation
Los Angeles, California, USA

Albert C.M. Ong, BM, BCh, MA, DM, FRCP, FAoP, FERA
University of Sheffield
Sheffield, UK

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

York P-C Pei, MSc, MD, FRCP(C), FACP, FASN
University of Toronto
Toronto, Ontario, Canada

Ronald D. Perrone, MD
Tufts University School of Medicine
Boston, Massachusetts, USA

Gopala K. Rangan, MBBS, FRACP, PhD, MBA
MDiagGenomics
Westmead Institute for Medical Research, The University of Sydney
Sydney, New South Wales, Australia

Brian Rayner, MBChB, FCP, MMED, PhD
University of Cape Town
Cape Town, South Africa

Roser Torra, MD, PhD
Fundació Puigvert
Barcelona, Spain

METHODS CHAIR

Reem A. Mustafa, MD, PhD, MPH
Department of Internal Medicine, Division of Nephrology and Hypertension
University of Kansas, Kansas City, Kansas, USA; and Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

KNOWLEDGE TRANSLATION LEAD

Edgar Lerma, MD, FCP, FASN
University of Illinois at Chicago
Advocate Christ Medical Center
Oaklawn, Illinois, USA

EVIDENCE REVIEW TEAM

Center for Evidence Synthesis in Health, Brown University School of Public Health, Providence, Rhode Island, 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, PhD, 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

Abstract

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD) represents the first KDIGO guideline on this subject. The scope includes topics such as nomenclature, diagnosis, prognosis, and prevalence; kidney manifestations; chronic kidney disease management and progression, kidney failure, and kidney replacement therapy; therapies to delay progression of kidney disease; polycystic liver disease; intracranial aneurysms and other extrarenal manifestations; lifestyle and psychosocial aspects; pregnancy and reproductive issues; pediatric issues; and approaches to the management of people with ADPKD. The guideline has been developed with patient partners, healthcare providers, and researchers around the world, using robust methodology. The goal of the guideline is to generate a useful resource for healthcare providers and patients by providing actionable recommendations based on a rigorous, formal, systematic literature review. Another aim is to propose research recommendations for areas in which gaps in knowledge are present. The guideline targets a broad audience of healthcare providers treating ADPKD, while taking into account implications for policy and payment. The development of this guideline followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, appraisal of the certainty of the evidence, and the strength of recommendations following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The guideline also provides useful infographics and practice points that serve to direct clinical care or activities for which a systematic review was not conducted. Limitations of the evidence are discussed, and areas for future research are presented.

Keywords: ADPKD; autosomal dominant polycystic kidney disease; evaluation; guideline; KDIGO; management

CITATION

In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). *Kidney Int.* 2025;107(2S):S1–S239.

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 it is the 4th most-common global cause for kidney replacement therapy (KRT). A Kidney Disease: Improving Global Outcomes (KDIGO) 2014 Controversies Conference on ADPKD 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 developing a clinical practice guideline for ADPKD.

Since 2014, genetic testing has become more accurate, readily available, affordable, and utilized. In addition to *PKD1* and *PKD2*, at least 7 genes 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 markers, 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 U.S., Canada, the Republic of Korea, Australia, and New Zealand. Long-acting somatostatin analogues are used increasingly 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 has published 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. The KDIGO Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD focuses on aspects of management that differ from those for other chronic kidney diseases, while referring to the other guidelines when appropriate. The guideline concentrates on clinical management questions that are addressed with high-certainty 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 made when a clinical question was not deemed to be a high priority for systematic review, to help readers implement the guidance from graded recommendations, and to issue "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, and 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 2014 Controversies Conference, as follows:

- 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 Progression of Polycystic Kidney Disease (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 includes 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 interventions such as long-acting somatostatin analogues, diet, and other pharmacologic agents.
- 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 their development and rupture.
- Chapter 7 includes practice points addressing diet, 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; screening for high BP; initiation of antihypertensive treatment; BP target and monitoring; optimal models of care; and the pediatric-to-adult transition.
- Chapter 10 stresses the importance of lifelong, 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 keeping the guideline relevant and patient-centered. We are indebted to all and hope that this guideline will help improve the care of people with ADPKD.

Olivier Devuyst, MD, PhD
Vicente E. 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 people with autosomal dominant polycystic kidney disease (ADPKD) or autosomal dominant polycystic liver disease (ADPLD) with a known genetic cause, a common nomenclature should include the disease name followed by the gene name.

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

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

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

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

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

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

1.2 Prevalence

1.2.1 Prevalence of ADPKD in kidney failure populations

[No recommendations or practice points]

1.3 Diagnosis

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

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

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

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

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

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

Ultrasound criteria by age group to ***diagnose*** ADPKD when there is a positive family history							
Age (years)	Number of cysts (test criterion based on number of cysts)	ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown gene type	
		Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive test (%)	Sn (%)
15–29	≥3 total	100	94	100	70	100	82
30–39	≥3 total	100	97	100	95	100	96
40–59	≥2 in each kidney	100	93	100	89	100	90
60+	≥4 in each kidney	100	100	100	100	ND	ND

Figure 3 | Ultrasound criteria by age group to diagnose autosomal dominant polycystic kidney disease (ADPKD) in people with a positive family history based on a positive predictive value of the test.[30] The sensitivity (Sn) of a test is its ability to designate an individual with the disease as positive. ND, not determined; PKD, polycystic kidney disease.

Ultrasound criteria by age group to ***exclude*** ADPKD when there is a positive family history							
Age (years)	Number of cysts (test criterion based on number of cysts)	ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown gene type	
		Predictive value based on a negative test (%)	Sp (%)	Predictive value based on a negative test (%)	Sp (%)	Predictive value based on a negative test (%)	Sp (%)
15–29	≥1 total	99	98	84	97	91	97
30–39	≥1 total	100	96	97	94	98	95
40–59	≥2 total	100	98	100	98	100	98

Figure 4 | Ultrasound criteria by age group to exclude autosomal dominant polycystic kidney disease (ADPKD) in people with a positive family history based on a negative predictive value of the test.[30] The specificity (Sp) of a test is its ability to designate an individual who does not have the disease as negative. PKD, polycystic kidney disease.

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

Magnetic resonance imaging (MRI) criteria for ages 16-40 years in people with a positive family history					
Age (years)	Number of cysts (test criterion based on number of cysts)	Predictive value based on a positive test (%)	Sensitivity (%)	Predictive value based on a negative test (%)	Specificity (%)
16–29	≥10 cysts	100	100		
30–40		100	100		
16–29	≥5 cysts			100	98.3
30–40				100	100

Figure 5 | Magnetic resonance imaging (MRI) criteria for ages 16–40 years in people with a positive family history.[31] The sensitivity of a test is its ability to designate an individual with the disease as positive. The specificity of a test is its ability to designate an individual who does not have the disease as negative.

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

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

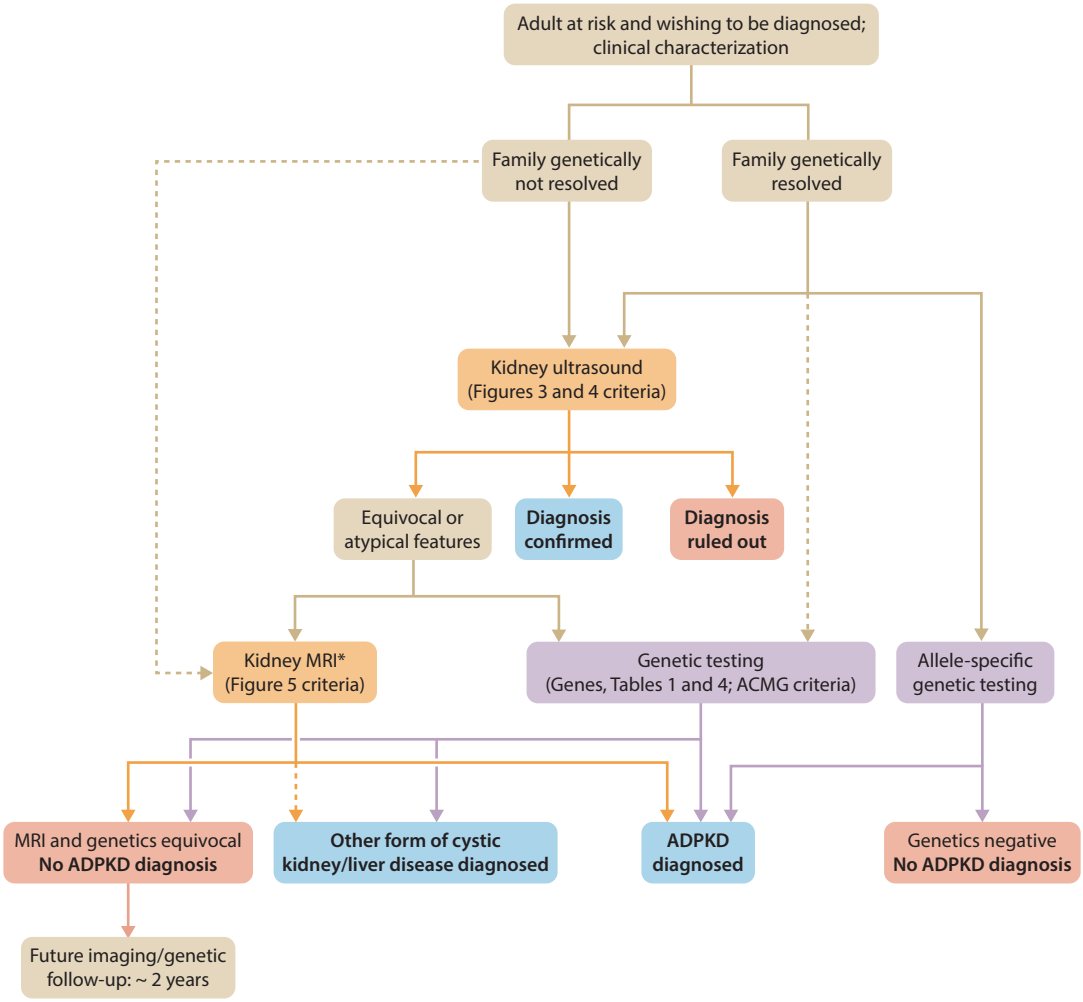


Figure 1 | Diagnosis algorithm in at-risk adults (positive family history) for autosomal dominant polycystic kidney disease (ADPKD). ACMG, American College of Medical Genetics and Genomics; MRI, magnetic resonance imaging. *Computed tomography, either with or without contrast, can also be used. Abdominal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

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

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

Table 4 | Situations in which genetic testing can clarify the diagnosis and aid in determining a prognosis

Situation	Genetic findings
Limited number of cysts	Positive result can show a genetic origin (minor gene or hypomorphic allele).
Variable disease severity in a family	Mosaicism or biallelic/digenic disease can explain some extreme variability.
Atypical findings with imaging, such as asymmetric or unilateral disease	Positive result can show a genetic origin (including mosaicism or minor gene involvement).
Discordance between structural (MIC) and functional (GFR) ADPKD severity[a]	Genetic testing may reveal an atypical form of the disease or additional genetic or contributory factors, but nongenetic factors may also be important.
Negative family history	Positive result can show a genetic origin (*de novo* mutation can be proven).
Very-early-onset (VEO) ADPKD	Biallelic disease may be found (Chapter 9).
Related living transplant donor (aged <30 yr, especially if a few cysts detected)	Genetic testing can exclude the familial variant, if known, and test for other genetic causes.
Family planning and preimplantation genetic diagnosis (PGD)	Obtaining a genetic diagnosis can aid in family planning and enable PGD (Chapter 8).
All people	Genetic testing can confirm the diagnosis, identify the responsible gene and variant, and provide prognostic information.

ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; MIC, Mayo Imaging Classification (see definition in Chapter 9); PGD, preimplantation genetic diagnosis.
[a]Discordance may be reduced GFR without significant kidney enlargement, or an older adult with large kidneys but normal GFR.
For more information about mosaicism, and biallelic and digenic inheritance, see Practice Point 1.3.12.

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

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

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

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

Table 5 | Other disorders that present with kidney cysts

Gene	Disease	Inheritance	Overlapping with ADPKD	Distinguishing from ADPKD	Comments
Developmental disorders					
HNF1B	*HNF1B*-related kidney disease	AD	Cystic kidney disease	Congenital kidney and urinary tract anomalies, early-onset diabetes, pancreatic disease, elevated liver enzyme levels, and hypomagnesemia	Sometimes presents as ADPKD spectrum alone
JAG1, NOTCH2	Alagille syndrome	AD	Kidney cysts	Hepatic bile duct paucity; cholestasis; cardiac, skeletal, facial, and eye abnormalities; and dysplastic kidneys	A major feature can be infantile, small cystic kidneys and abnormal kidney function.
Collagen disorders					
COL4A1	Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)	AD	Kidney cysts	Hematuria, retinal arterial tortuosities, muscular contractures, and brain small-vessel disease	Presentation with mild cystic disease and few other phenotypes has been described.[93,99,100]
COL4A3, COL4A4, COL4A5	COL4A-related diseases	AD and X-linked	Kidney cysts	Thinning of the glomerular basement membrane, microhematuria	Occasionally, kidney cysts are the major presentation.[93,94]
Urinary stone diseases (USD)					
CYP24A1, SLC34A3, HOGA1	A variety of USDs	AR (AD)	Kidney cysts	Predominant phenotype of kidney stones, nephrocalcinosis, and/or other mineralization	Usually limited cyst involvement[101–103]; may apply to other USDs
Autosomal dominant tubulointerstitial kidney disease (ADTKD)					
MUC1, REN, SEC61A1, UMOD	ADTKD	AD	Kidney cysts	Reduced kidney function, normal- to small-sized kidneys due to fibrotic kidneys; a few kidney cysts may be detected; no liver cysts	Hyperuricemia (low FE_{urate}) and gout are prominent in ADTKD-*UMOD* and anemia and gout in ADTKD-*REN*.
Recessive PKD					
PKHD1, DZIP1L, CYS1, PKD1	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 (CHF) rather than PLD	Later-onset kidney disease can mimic ADPKD, but kidneys usually do not increase in length over time and CHF is usually present. Biallelic *PKD1* changes can cause VEO to adult-onset disease.
PMM2	Hyperinsulinemic hypoglycemia and polycystic kidney disease (HIPKD)	AR	Kidney cysts	The kidney disease is ARPKD-like, but hyperinsulinemic hypoglycemia is also found; liver cysts are only rarely seen	Biallelic disease where at least one allele is the promoter variant (c.-167G>T); typical biallelic *PMM2* disease causes the congenital disorder of glycosylation type 1a (CDG1A)
Tumorous disorders					
FLCN	Birt-Hogg-Dubé syndrome	AD	Kidney cysts	Hair follicle hamartomas, kidney tumors, spontaneous pneumothorax, lung cysts	*FLCN* pathogenic variant described in person with "ADPKD" and lung cysts[88]
TSC1 TSC2	Tuberous sclerosis complex (TSC)	AD	Kidney cysts	Multisystem disorder with hamartomas in brain, skin, heart, kidneys (angiomyolipomas), and/or lung, plus CNS manifestations: epilepsy, learning difficulties, behavioral problems	Kidney cysts can be a major presentation with limited additional phenotypes.
PKD1/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 KF; mosaicism is common, which may be associated with less severe PKD[90,91]
VHL	Von-Hippel-Lindau syndrome	AD	Kidney and pancreatic cysts	Familial cancer syndrome with malignant and benign neoplasms in retina, cerebellum, spinal hemangioblastoma, RCC, pheochromocytoma, and pancreatic tumors	RCC develops from the kidney cysts.

Table 5 | (Continued)

Gene	Disease	Inheritance	Overlapping with ADPKD	Distinguishing from ADPKD	Comments
FH	Hereditary leiomyomatosis and renal cell cancer (HLRCC)	AD	Small kidney cysts	Papillary RCC, leiomyomata of the uterus, and cutaneous piloleiomyoma	Kidney cysts that can metastasize at a small size
Syndromic ciliopathies					
OFD1	Oral-facial-digital syndrome 1	X-linked	Kidney cysts in female patients	Malformations of the face, oral cavity, including cleft lip/palate, and digits, and PKD with abnormal kidney function; usually, lethal in male patients	The PKD can mimic ADPKD, and the facial and digital phenotypes can be minimal.
NPHP1 and other NPHP genes	Nephronophthisis (NPHP)	AR	Cortico-medullary cysts	Childhood presentation with echogenicity, loss of corticomedullary differentiation, small atrophic kidneys, and CKD	NPHP1, and other forms of NPHP, can first present in adulthood.
Many genes	Syndromic ciliopathies such as Joubert, Bardet Biedl, Meckel syndrome, and short rib thoracic dystrophy	AR	Kidney cysts	Often infantile or childhood disorders; a wide range of extrarenal 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 KF; kidneys are not enlarged	ACD is a risk factor for kidney cancer.

ACD, acquired cystic disease; AD, autosomal dominant; AR, autosomal recessive; CHF, congenital hepatic fibrosis; CKD, chronic kidney disease; CNS, central nervous system; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; RCC, renal cell carcinoma; TSC, tuberous sclerosis complex; USD, urinary stone diseases; VEO, very early onset.

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

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

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

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

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

1.4 Prognostics

1.4.1 Factors associated with the severity of kidney disease in ADPKD

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

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

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

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

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

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

1.4.2 Ways to assess the severity of kidney disease progression

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

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

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

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

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

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

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

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

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

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

Chapter 2: Kidney manifestations

2.1 High blood pressure

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

Hypertension in ADPKD		
Monitoring	**Non-pharmacologic interventions**	**Medical management**
• Standardized office BP measurement in preference to routine office BP measurement • HBPM is preferred to office only measurements • Consider ABPM in children and adults with difficult BP control, LVH, proteinuria, or declining kidney function but normal office BP readings • Consider work up for secondary high BP when >3 BP medications are needed in the setting of medication and dietary compliance	• Reduce dietary sodium including minimizing processed foods • Optimize body weight with a healthy diet and regular exercise • Optimize pain management	• Inhibition of RAS provides the cornerstone of BP management and includes the use of an ACEi or ARB • Optimize BP with a 2nd-line agent, if needed • Individualized therapy is indicated

Figure 14| Blood pressure (BP) management in autosomal dominant polycystic kidney disease (ADPKD). ABPM, ambulatory BP-monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HBPM, home BP-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.[215]

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

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

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

Practice Point 2.1.3: Healthy dietary and lifestyle interventions should be incorporated into 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 of ≤110/75 mm Hg, as measured by HBPM, if tolerated (*1D*).

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

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

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 that this recommendation should apply to people with ADPKD.[215]

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

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

2.2 Chronic kidney pain

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

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

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

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

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

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

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

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 their medical records should be reviewed.

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

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

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.[252] Although 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* for the general population apply to people with ADPKD.[262] Although 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 (540 μmol/l), or urolithiasis, we conditionally recommend initiating ULT.

Recommendation 2.4.3: For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl or 408 μmol/l 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/d [and lower in patients with CKD] for allopurinol or ≤40 mg/d 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

Practice Point 2.4.1: **People with ADPKD should not be treated pharmacologically for asymptomatic hyperuricemia. However, lifestyle and dietary modification may be beneficial (see *2020 American College of Rheumatology Guideline for the Management of Gout*[262]).**

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

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

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

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.[268] Although 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).

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

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

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 16).

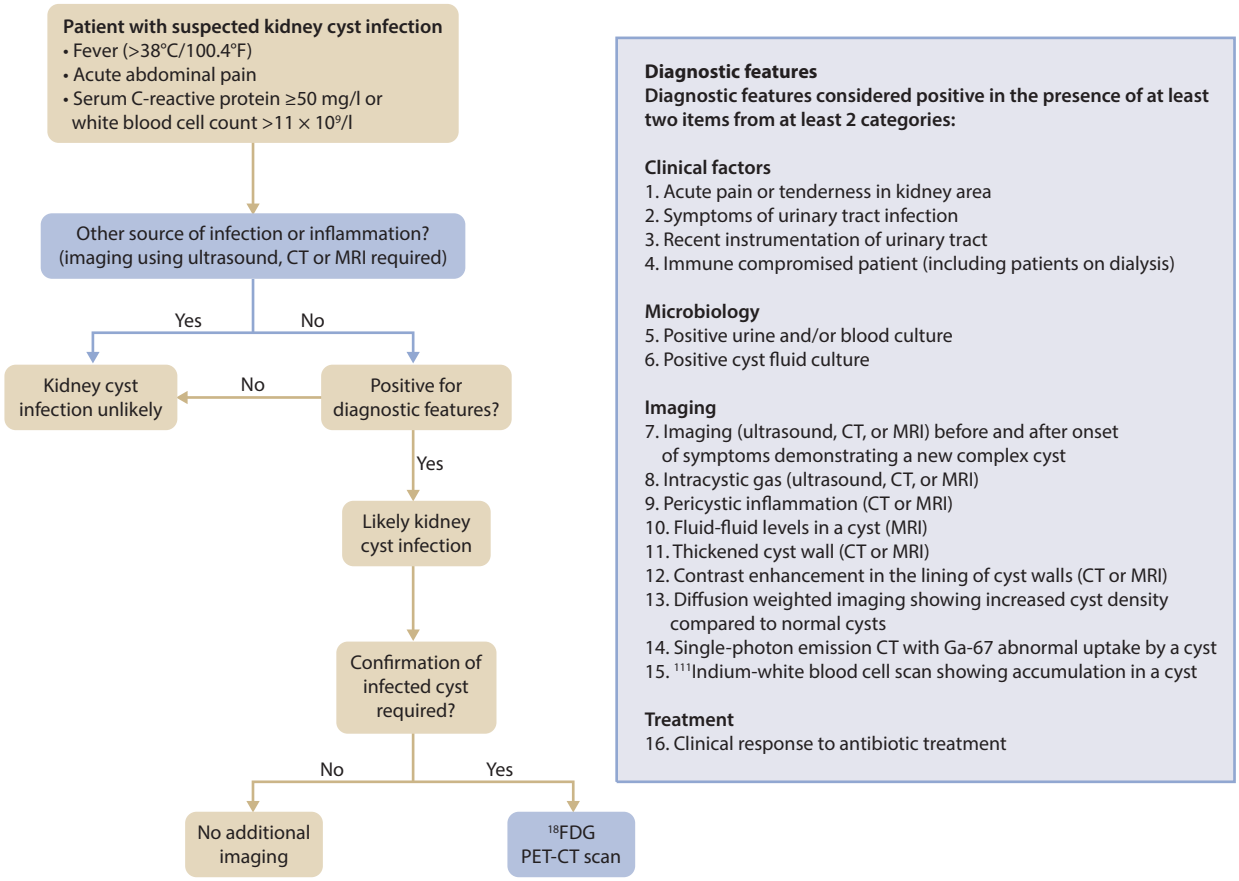


Figure 16 | Diagnostic algorithm for an infected kidney cyst in autosomal dominant polycystic kidney disease. CT, computed tomography; ^{18}FDG PET-CT, positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with computed tomography; Ga-67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga *et al.*[269]

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

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

2.7 Renal cell carcinoma

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

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

Chapter 3: Chronic kidney disease (CKD) management and progression, kidney failure, and kidney replacement therapy (KRT)

3.1 CKD management and progression

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

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

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

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

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*.[277]

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

3.2 Kidney transplantation

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

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

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

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

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

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

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

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

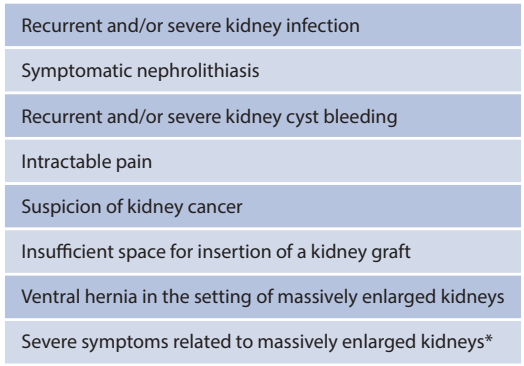


Figure 21 | Potential indications for native nephrectomy in people with autosomal dominant polycystic kidney disease receiving a kidney transplant. *People with chronic kidney disease should be asked for pain- and volume-related complaints in a structured manner.

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

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

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

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

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

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

3.3 Kidney replacement therapy

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

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

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

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

Chapter 4: Therapies to delay the progression of kidney disease

4.1 Tolvaptan

4.1.1 Indications for tolvaptan in ADPKD

Recommendation 4.1.1.1: We recommend initiating tolvaptan treatment in adults with ADPKD with an estimated glomerular filtration rate (eGFR) ≥25 ml/min per 1.73 m^2 who are at risk for rapidly progressive disease (Figure 25) (*1B*).

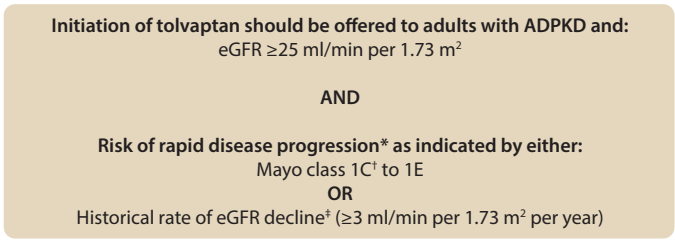


Figure 25 | The Kidney Disease: Improving Global Outcomes algorithm to decide in whom to prescribe tolvaptan. *Rapid disease progression is defined as having reached or being expected to reach kidney failure due to autosomal dominant polycystic kidney disease (ADPKD) before age ∼60 years, the average age at which untreated people with ADPKD reach kidney failure. The use of age ∼60 years is based on multiple cohort studies (not stratified by genotype) (European Renal Association–European Dialysis and Transplant Association [ERA-EDTA], mean age 58 years[379]; Genkyst cohort, 61.7 years[36]; Mayo PKD Database, 62 years[380]; Korea national cohort, 62 years[379]; and Australia and New Zealand Dialysis and Transplant Registry (ANZDATA registry), 60 years.[381] †Because some people with MIC subclass 1C may not have rapid disease progression, clinical judgment and evaluation should be made on a case-by-case basis and additional information could be used, particularly in the people with age-adjusted height-adjusted total kidney volume (htTKV) on the borderline of Mayo Image Classification 1B, to assess the risk for rapid disease progression (e.g., evidence of estimated glomerular filtration rate [eGFR] decline or of a reduced age-calibrated eGFR,[382] Predicting Renal Outcome in Polycystic Kidney Disease [PROPKD] score >6, family history with onset of kidney replacement therapy [KRT] at <60 years in ≥2 first-line family members, or novel biomarkers).[202] ‡If estimated glomerular filtration rate (eGFR) loss has likely alternative explanations (e.g., vascular disease, uncontrolled hypertension, diabetic nephropathy, proteinuria ≥1 g/d) and/or acute kidney injury, then initiation of tolvaptan use should be re-evaluated, even in the presence of rapid eGFR decline. In these cases, additional information (including magnetic resonance imaging or computed tomography imaging should be undertaken, if not previously performed; PROPKD score >6, a family history with onset of KRT at age <60 years in ≥2 first-line family members) should be acquired to ensure ADPKD as the primary reason for eGFR loss.

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

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

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

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

4.1.2 Precautions for tolvaptan use in ADPKD

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

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

4.1.3 Dosage of tolvaptan

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

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

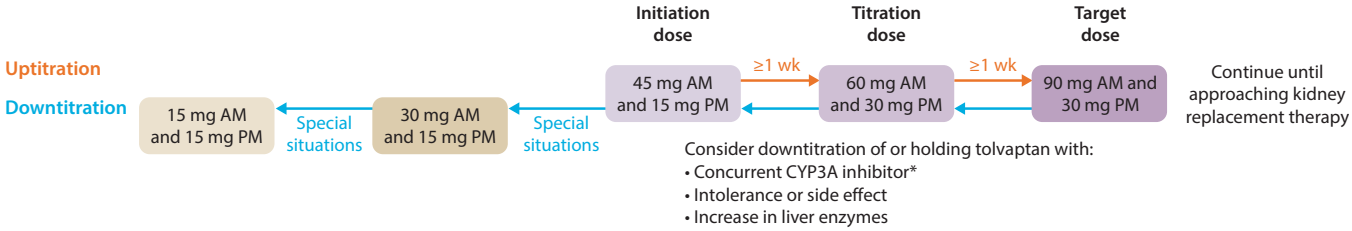


Figure 28 | Commencement of and titration approach to tolvaptan use in autosomal dominant polycystic kidney disease. *Examples of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (reduce clearance by >80%) are as follows: antifungals (itraconazole, ketoconazole); antibiotics (clarithromycin);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

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 use should be discontinued prior to pregnancy, during lactation, and prior to the commencement of KRT.

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

4.1.4 Counseling people with ADPKD who are receiving tolvaptan

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

Practice Point 4.1.4.2: Education should be provided to people with ADPKD regarding the effect of tolvaptan to increase urinary water loss (such as thirst, polyuria, nocturia, and pollakiuria), the need to drink enough water to replace urinary losses, as well as strategies to minimize and manage anticipated aquaretic effects to ensure long-term tolerability.

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

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

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.

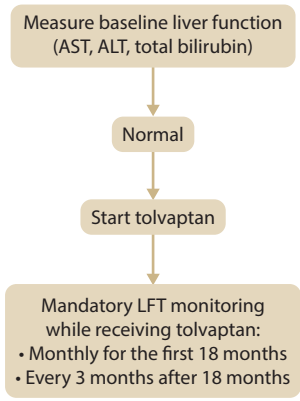


Figure 29 | Recommended monitoring for the early detection of drug-induced liver injury in people with autosomal dominant polycystic kidney disease on chronic treatment with tolvaptan. Note: In some countries, regulatory authorities recommend monitoring liver function tests (LFTs) at 2 and 4 weeks in the first month after starting tolvaptan use. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

4.1.6 Management and risk mitigation of aquaretic side effects

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

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

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

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

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

4.2 Water intake in the absence of tolvaptan

4.2.1 General advice regarding water intake

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

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

4.2.2 Precautions regarding increasing water intake

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

Practice Point 4.2.2.2: People with CKD G4–G5 (eGFR <30 ml/min per 1.73 m^2) 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 (mTOR) inhibitors

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

4.4 Statins

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

4.5 Metformin

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

4.6 Somatostatin analogues

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

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

4.7 Sodium-glucose co-transporter-2 inhibitors (SGLT2i)

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

4.8 Ketogenic interventions

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

4.9 Complementary medicines

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

Chapter 5: Polycystic liver disease

5.1 Diagnosis and staging of PLD

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

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

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

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

5.2 Risk factors

5.2.1 Female sex hormones

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

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 (Table 13).

Table 13 | Methods to assess sarcopenia and malnutrition

Technique	Definition of sarcopenia or malnutrition
Skeletal muscle index	• Skeletal muscle mass measured at 3rd lumbar vertebrae. Sarcopenia defined as SMI <38.5 cm^2/h^2 in female patients, and <52.4 cm^2/h^2 in male patients
Bioelectrical impedance analysis	• Sarcopenia: • <5.7 kg/m^2 in female patients • <7.0 kg/m^2 in male patients
Grip strength	• Sarcopenia: • Female patients, <18 kg • Male patients, <26 kg
Mid-arm circumference	• Severe malnutrition: • Female patients: <23.1 cm • Male patients: <23.8 cm
Detailed nutritional assessment	• Includes: clinical examination (history and physical examination), anthropometric measurements, diagnostic tests (laboratory tests and body composition studies) and dietary assessment

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.

5.2.3 Management

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

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

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

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

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

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

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

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

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).

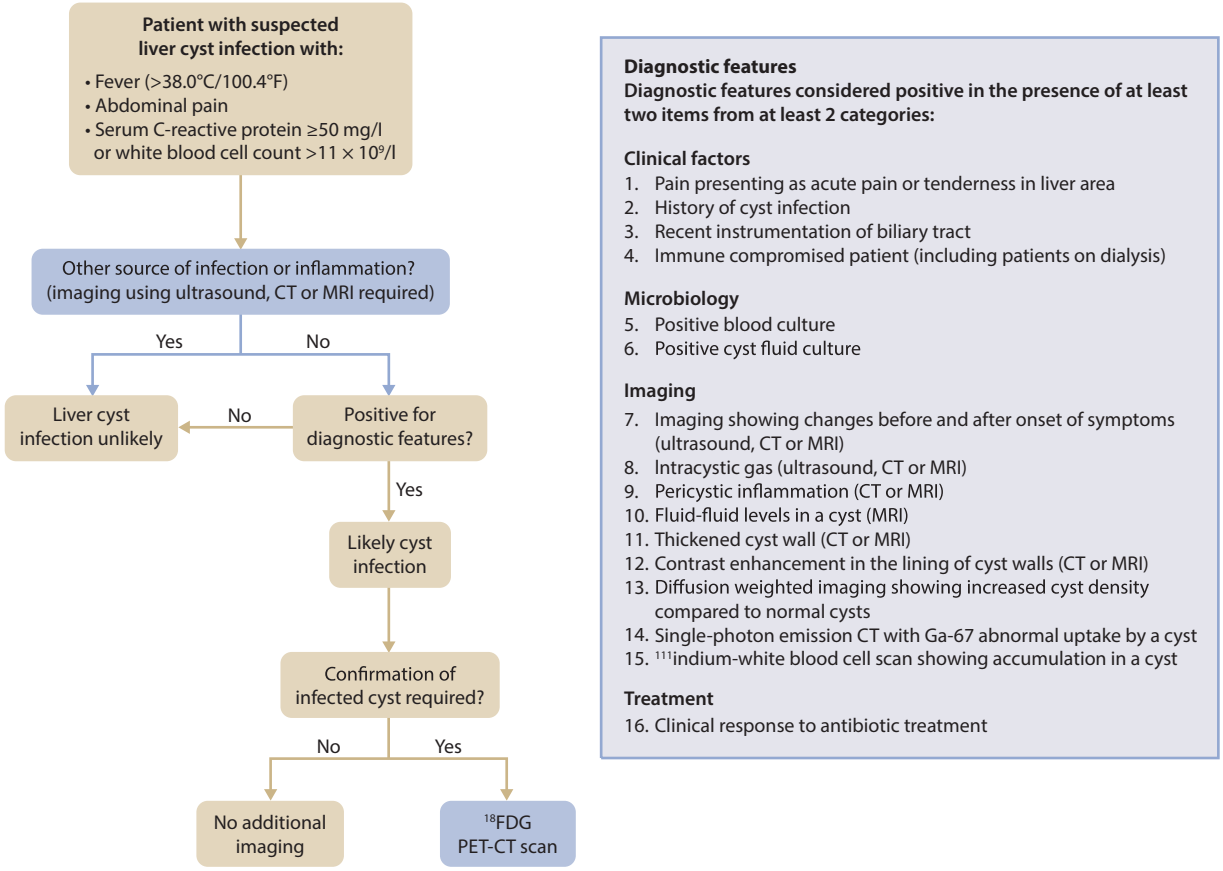


Figure 33 | Diagnostic algorithm to diagnose liver cyst infections in autosomal dominant polycystic kidney disease. CT, computed tomography; ^{18}FDG PET-CT, positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with computed tomography; Ga-67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga *et al.*[269]

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

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

5.3.2 Management

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

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

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

Practice Point 5.3.2.4: Percutaneous drainage of infected liver cysts <48 hours after initiation of antibiotics may be reasonable in the presence of the following:

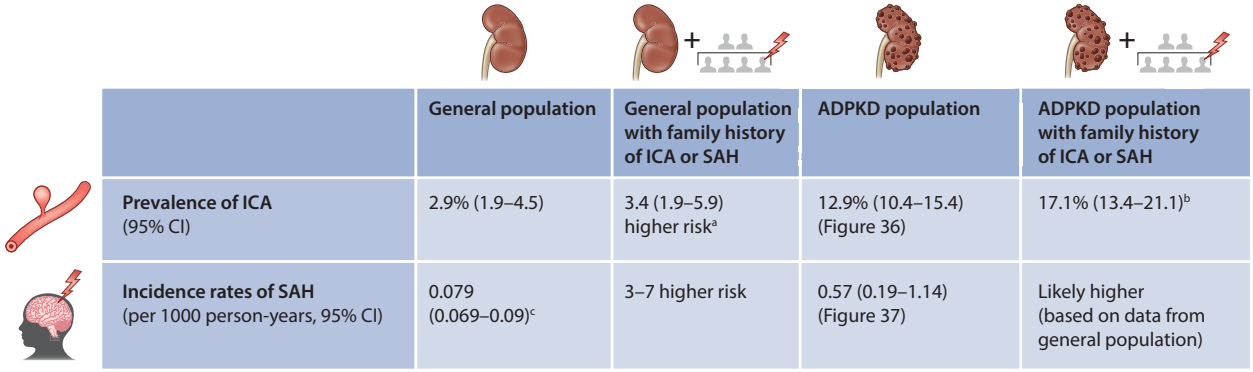
- isolation of pathogens that are unresponsive to antibiotic therapy from a cyst aspirate;
- immunocompromise in the patient;
- large infected hepatic cysts (>8 cm); or
- hemodynamic instability and/or signs of sepsis.

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

Chapter 6: Intracranial aneurysms and other extrarenal manifestations

6.1 Intracranial aneurysms

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



	General population	General population with family history of ICA or SAH	ADPKD population	ADPKD population with family history of ICA or SAH
Prevalence of ICA (95% CI)	2.9% (1.9–4.5)	3.4 (1.9–5.9) higher risk[a]	12.9% (10.4–15.4) (Figure 36)	17.1% (13.4–21.1)[b]
Incidence rates of SAH (per 1000 person-years, 95% CI)	0.079 (0.069–0.09)[c]	3–7 higher risk	0.57 (0.19–1.14) (Figure 37)	Likely higher (based on data from general population)

Figure 35 | Prevalence of unruptured intracranial aneurysms (ICAs) and incidence of subarachnoid hemorrhage (SAH) in the general and autosomal dominant polycystic kidney disease (ADPKD) populations, overall and in the presence of a family history of ICA or SAH. CI, confidence interval. [a]Prevalence ratio compared with no family history, age- and sex-adjusted. [b]Based on Evidence Review Team meta-analysis of 7 studies.[430,572–577] [c]Overall crude SAH incidence across midyear period. References: Top row, from left to right: Box 1 and 2: Vlak *et al.*[578]; Box 3: see Figure 36. Box 4: Sanchis *et al.*[576] and Xu *et al.*[577] Bottom row, from left to right: Box 5 and 6: Etminan *et al.*[579] and Rinkel and Ruigrok.[580] Box 7: see Figure 37.

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

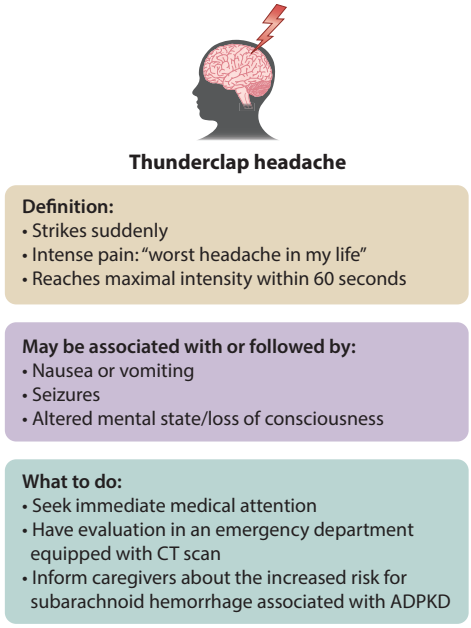


Figure 38| Specific presentation of thunderclap headache and suggested actions. ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography.

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

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

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

Practice Point 6.1.5: **People with ADPKD should be informed of the implications of ICA screening, as highlighted in Table 16.**

Table 16| Advantages and limitations of screening for ICAs

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

ICA, intracranial aneurysm.

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

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

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

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

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

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

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

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

6.2 Other vascular associations

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

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

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

6.3 Cardiac associations

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

6.4 Abdominal wall hernia

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

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

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

6.5 Other extrarenal manifestations

[No recommendations or practice points]

Chapter 7: Lifestyle and psychosocial aspects

7.1 Nutrition intake

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

Table 18 | Nutrition guidance for people with ADPKD and CKD G1–G4

	Recommended daily intake	Comments and impact on ADPKD
Water	≥2 l/d Maintain morning urine osmolality <280 mOsm/kg[a]	• High water intake prevents kidney stones and may reduce kidney function loss.[485] • May need to adjust daily intake depending on concomitant medications and capacity to dilute the urine to minimize the risk of hyponatremia • Refer to Chapter 4 for more details.
Salt	Sodium <2 g/d (equivalent to <90 mmol sodium/d or <5 g salt/d)	• Recommended by WHO for the general population[683] • High salt intake in the observational CRISP study and in *post hoc* analyses of clinical trials in people with ADPKD has been associated with faster increase in kidney volume and, at later stages (eGFR 25–60 ml/min per 1.73 m^2), with faster decline in kidney function.[141,142,684] • People with ADPKD should be counseled against adding salt to their food, and to avoid processed foods (typically high in sodium) as much as possible.
Protein	0.8–1 g/kg (weight)/d	• Recommended by WHO for the general population[485,683] • No benefit of protein restriction has been demonstrated; however, excess dietary protein (≥1.3 g/kg/d) may be harmful.[485] • Plant-based proteins are preferred to animal proteins from red and processed meat.[685]
Calories	25–35 kcal/kg/d	• High BMI and obesity are associated with many adverse health conditions and may be associated with accelerated ADPKD progression.[140,683,686] • Individualized to prevent or treat overweight and obesity
Fat	<30% of daily energy intake (70 g/d [F], 87 g/d [M])	• Recommended for the general population[687,688] • Saturated fat limited to <10% of total fat
Fiber	25–38 g/d (14 g per 1000 calories)	• Recommended for the general population[689–691]
General	A well-balanced diet[690] High in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts Low in processed meats, refined sugar, and sugar-sweetened beverages	• Recommended by WHO for the general population[692] • At least 400 g (5 portions/d) of fruit and vegetables, excluding high-starch foods such as potatoes[692] • Minimize the intake of added sugars and sugar-sweetened beverages, aiming to limit free sugars to <10% of total energy intake, and ideally to 5%.[692]
Stone prevention		• Specific dietary assessment and recommendations for the prevention of kidney stones (Recommendation 2.3.3)[693]

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CKD, chronic kidney disease; CRISP, Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease; eGFR, estimated glomerular filtration rate; F, female; M, male; TKV, total kidney volume; WHO, World Health Organization.
[a]Using second morning urine sample.

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

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

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

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

$$\text{Adjusted BMI (ADPKD)} = \frac{\text{Adjusted body weight (kg)}^*}{\text{Height (m)}^2}$$

$$^*\text{Adjusted body weight} = \text{Measured body weight (kg)} - \text{TKV (in kg)} - \text{TLV (in kg)} + \text{weight of normal kidneys (kg)}^\dagger \text{ and liver (kg)}^\dagger$$

Figure 20 | Calculations for adjusted body mass index (BMI) in people with autosomal dominant polycystic kidney disease (ADPKD). TKV, total kidney volume; TLV, total liver volume. *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; 1 liter of volume is assumed to equal 1 kg of weight. Normal kidney and liver weights vary with age and BMI (https://pathology.oit.duke.edu/siteParts/Typical%20Organ%20Weights.pdf). †A reasonable approximation for total kidney weight is 0.27 kg for men and 0.23 kg for women; for liver, a reasonable approximation is 1.6 kg for men and 1.3 kg for women.

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

Practice Point 7.1.7: People with ADPKD with poor oral intake due to organomegaly or advanced CKD (CKD G4–G5) should be evaluated for malnutrition and 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 for at least 1 hour, twice per week.

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

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

7.3 Lifestyle management

7.3.1 Tobacco

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

7.3.2 Alcohol

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

7.3.3 Caffeine

[No recommendations or practice points]

7.3.4 Cannabis products

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

7.3.5 Nephrotoxins

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

7.4 Psychosocial care

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

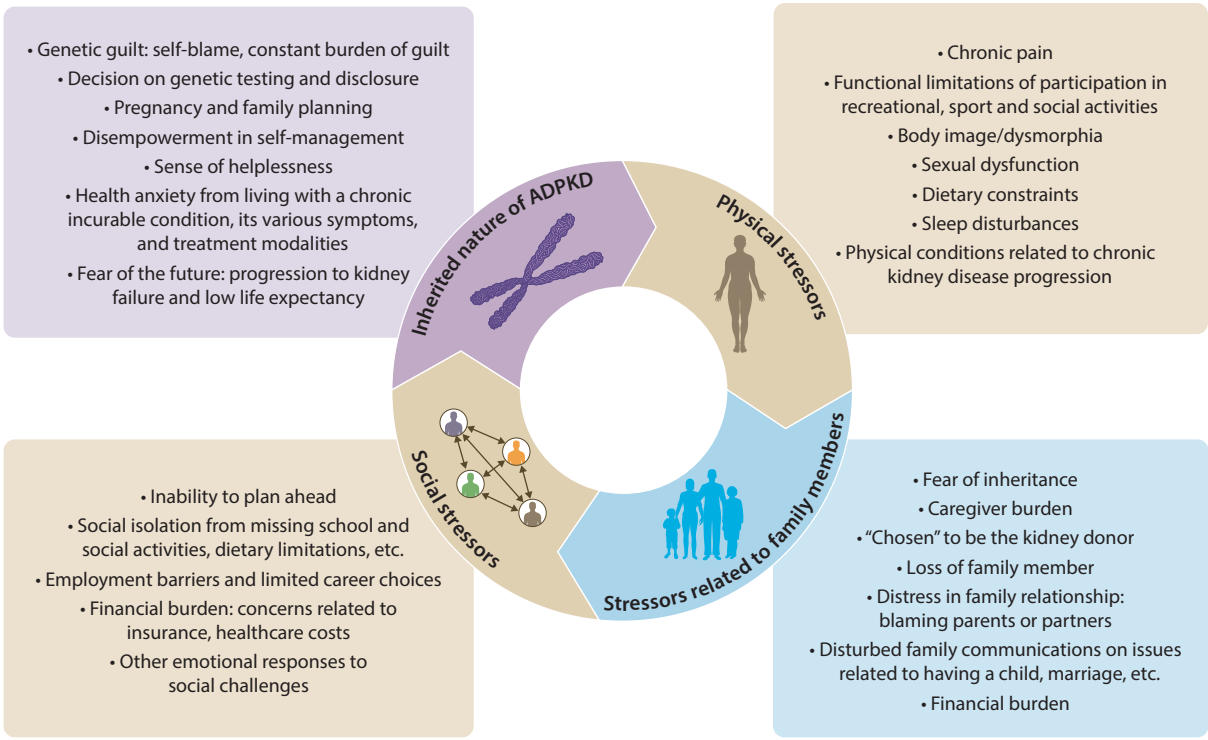


Figure 42 | Stressors associated with psychosocial issues in people with autosomal dominant polycystic kidney disease (ADPKD).

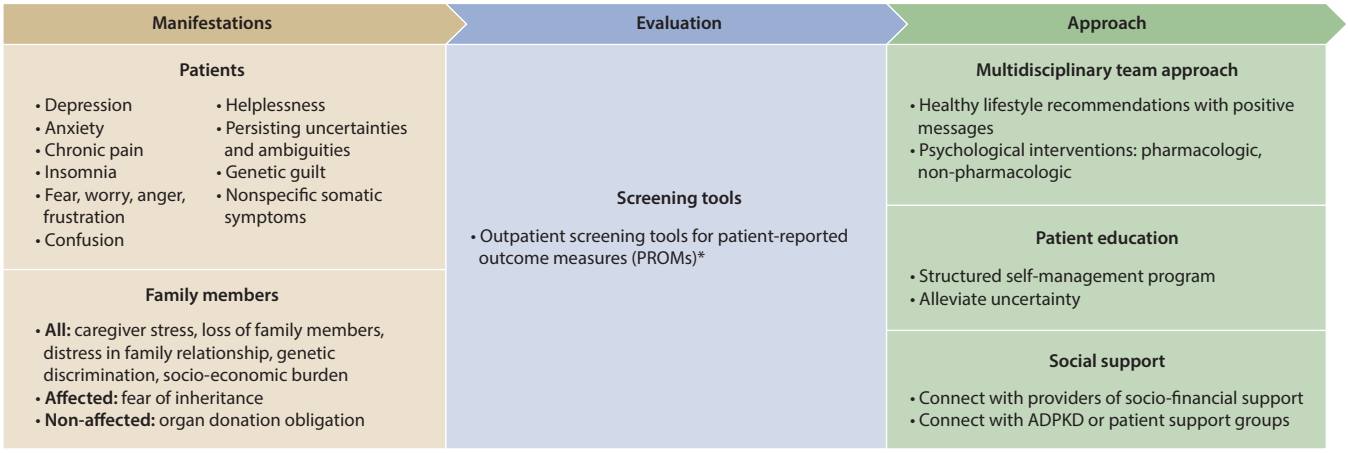


Figure 43 | Psychosocial manifestations, screening, and approach. ADPKD, autosomal dominant polycystic kidney disease. *See Appendix 1.

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

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

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

Chapter 8: Pregnancy and reproductive issues

8.1 Management of women with ADPKD

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

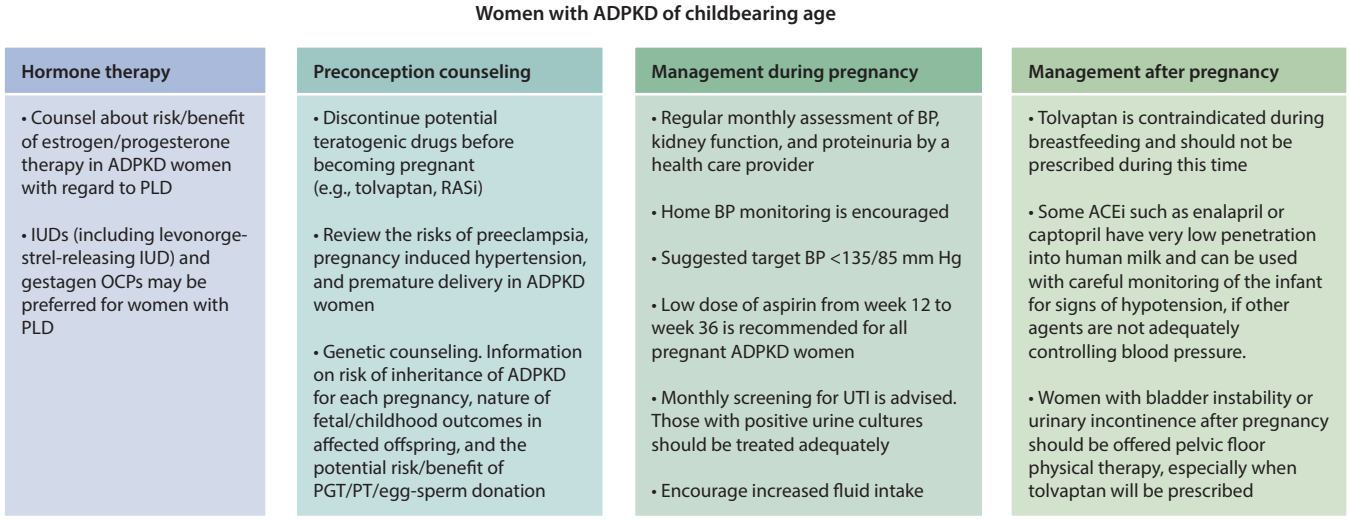


Figure 45 | Management of women with autosomal dominant polycystic kidney disease (ADPKD) of childbearing age. ACEi, angiotensin-converting enzyme inhibitor; BP, blood pressure; IUD, intrauterine device; OCP, oral contraceptive; PGT, preimplantation genetic test; PLD, polycystic liver disease (>10 cysts in the liver); PT, prenatal test; RASi, renin–angiotensin system inhibitors; UTI, urinary tract infection.

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

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

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

8.2 Preconception counseling

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

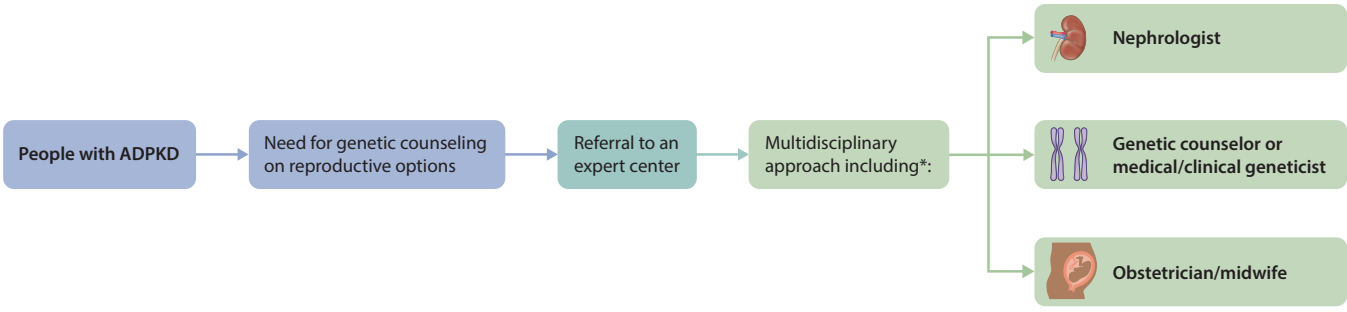


Figure 46 | Multidisciplinary approach to preconception counseling. ADPKD, autosomal dominant polycystic kidney disease. *Other specialties may be involved, depending on the case (e.g., hepatologist, neurologist).

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

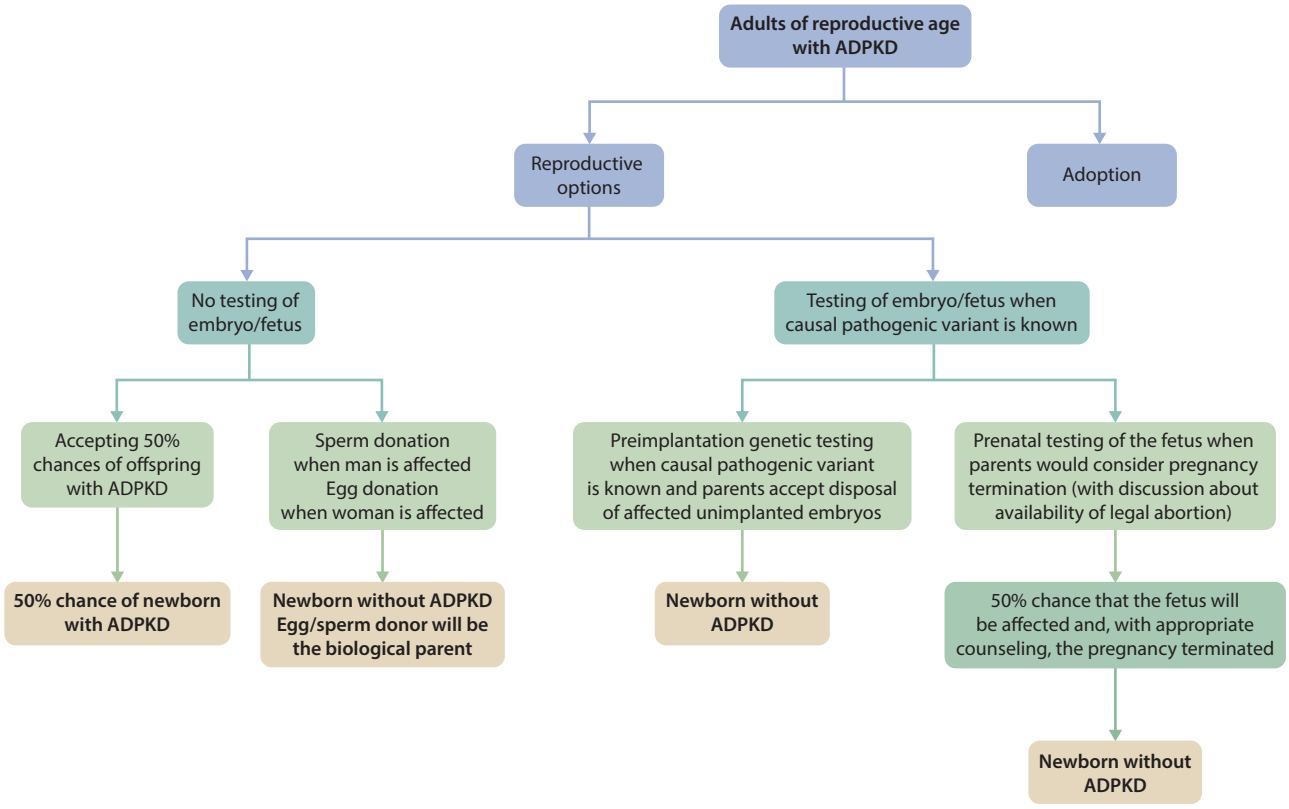


Figure 47 | Reproductive options for men and women with autosomal dominant polycystic kidney disease (ADPKD).

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

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

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

8.3 Pregnant women with ADPKD

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

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

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

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

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

8.4 Hypertension in pregnancy

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

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

8.5 Preeclampsia

Practice Point 8.5.1: Women with ADPKD are at an increased risk of preeclampsia and preterm delivery and should be monitored carefully throughout their pregnancy and in the postpartum period. Assessment of the sFlt-1/PlGF ratio in plasma, from 24 weeks of gestation and every 4–6 weeks, should be done to rule out preeclampsia.

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 ADPKD in the child. In this setting, shared decision-making regarding the value and short- and long-term implications of confirmatory genetic testing is advised.

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

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

8.7 Postpartum care

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

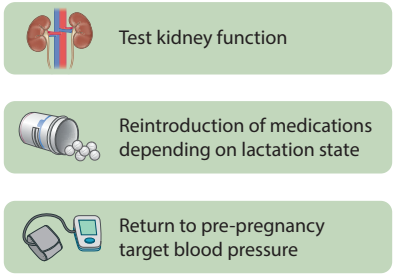


Figure 49 | Postpartum kidney review.

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

Chapter 9: Pediatric issues

9.1 Diagnosis of ADPKD in children

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

Table 21 | Definitions of phenotypical entities in children with ADPKD

Subentity	Definition
VEO-ADPKD	Symptoms or clinical evidence of severe ADPKD **at age <18 mo** defined by: • antenatal diagnosis of hyperechogenic enlarged kidneys (>2 SD for gestational age) with oligohydramnios, OR • enlarged cystic kidneys (>2 SD for age, sex, height) between birth and age 18 mo with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR
EO-ADPKD	Symptoms or clinical evidence of severe ADPKD **between ages 18 mo and 15 yr** determined by: • presence of enlarged cystic kidneys (>2 SD for age, sex, and height) between ages 18 mo and 15 yr with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR
Child with ADPKD	A child with diagnosis of **ADPKD not fulfilling VEO-ADPKD or EO-ADPKD criteria**
Child at risk of ADPKD	A child **with potential for heritability of ADPKD in the setting of a relative known to have ADPKD**

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; EO, early onset; VEO, very early onset.

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

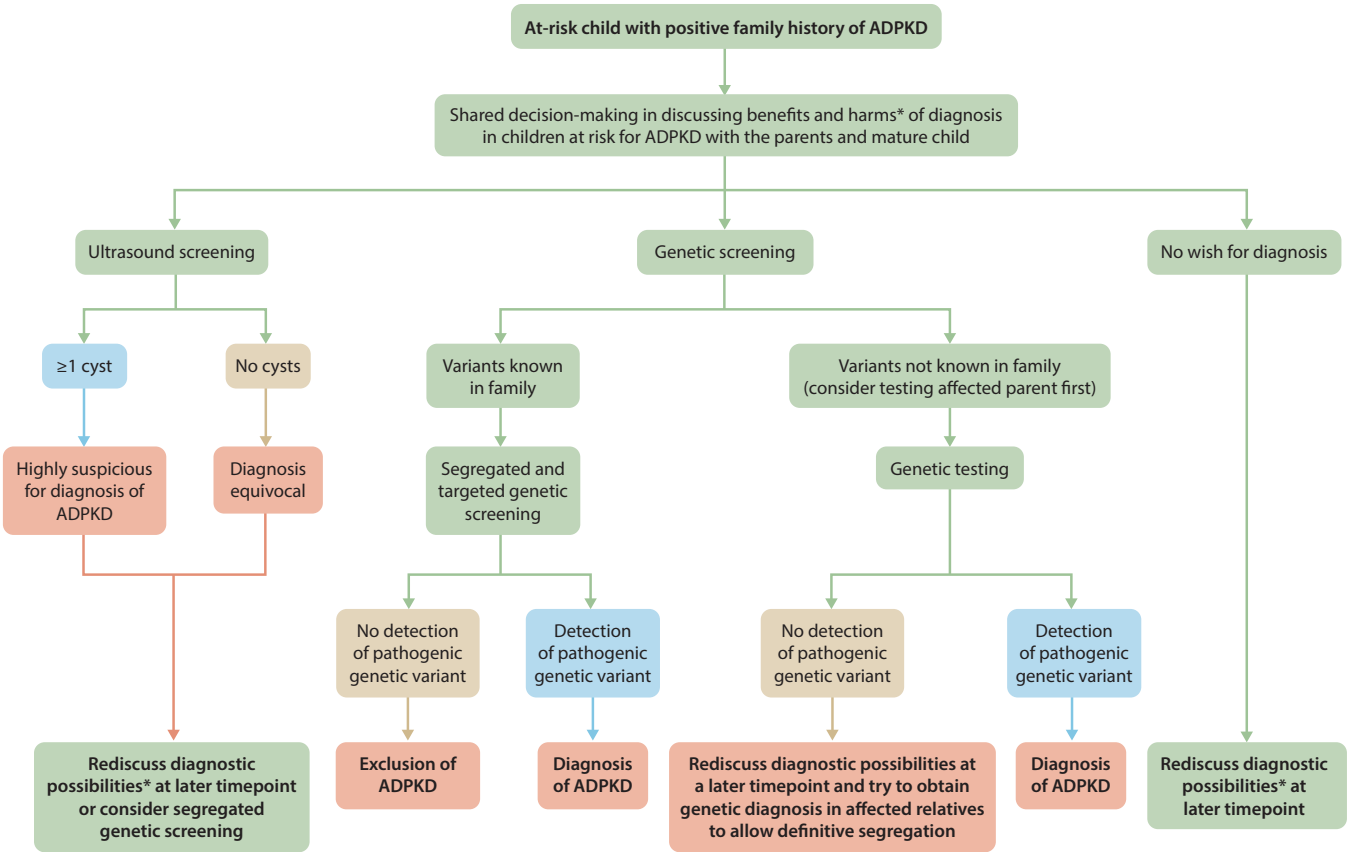


Figure 50 | Diagnosis of children at risk of autosomal dominant polycystic kidney disease (ADPKD), which should be performed by a pediatrician with expertise in ADPKD. *See Table 3.

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

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

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

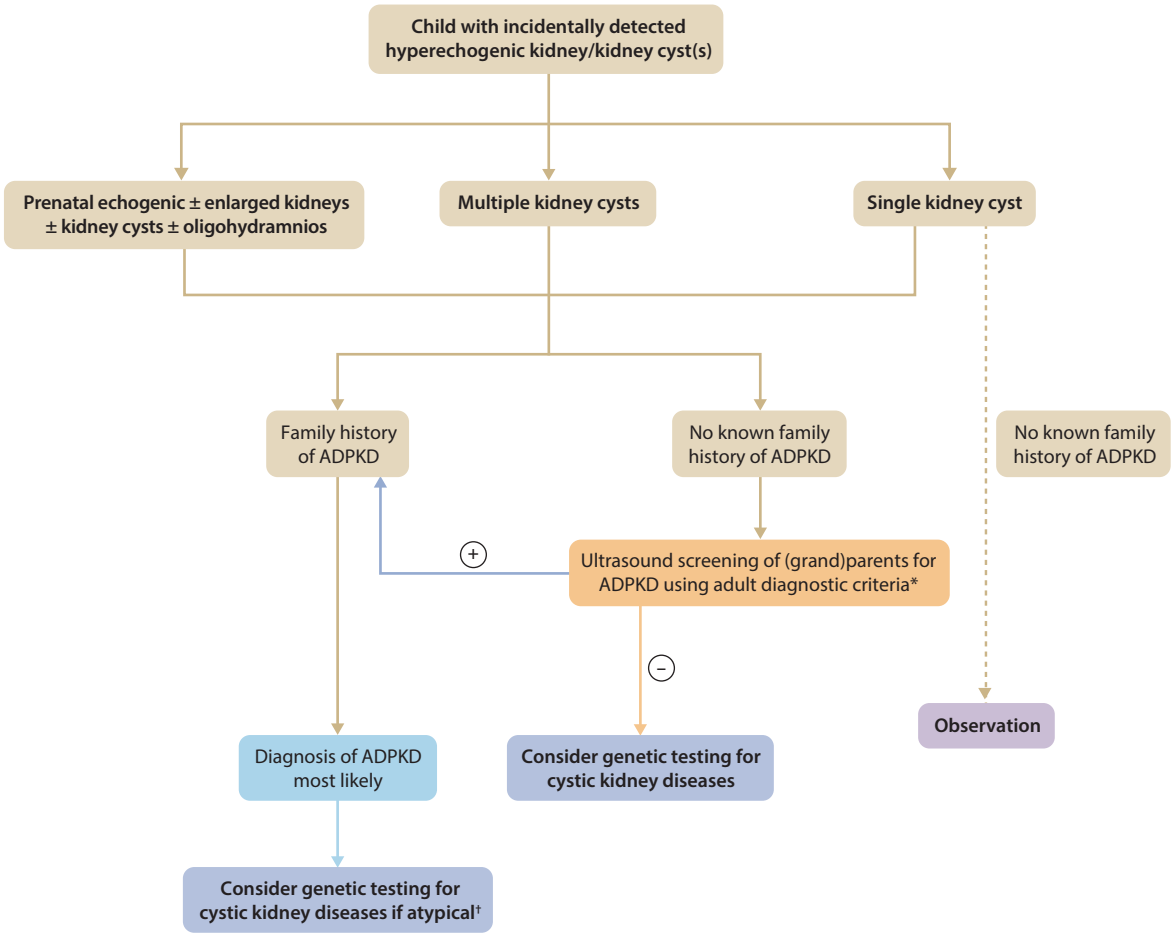


Figure 51 | Diagnosis of children with clinical consideration of autosomal dominant polycystic kidney disease (ADPKD). Dash lines denote other pathway for consideration. *Consider screening grandparents if parent screening is negative or parents are aged<40 years. †For example, very early onset ADPKD; severe kidney involvement relative to age.

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 51).

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

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

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

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

9.2 BP control in children and adolescents with ADPKD

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

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

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

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

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

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

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

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

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

9.3 Follow-up assessment in children with ADPKD

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

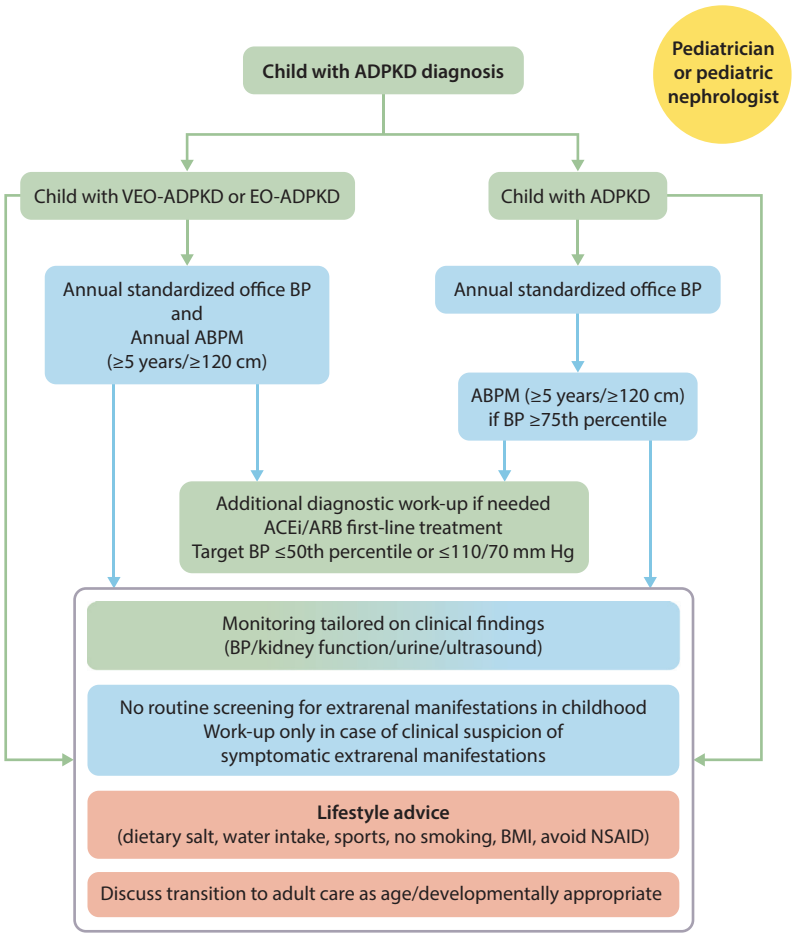


Figure 52 | Follow-up of children with autosomal dominant polycystic kidney disease (ADPKD), which should be performed by a pediatrician or pediatric nephrologist. ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body 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; or ICA in children and adolescents with ADPKD (Figure 52). Apply screening recommendations from adulthood (Chapter 6).

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

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

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

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

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

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

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

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

9.4 Diet and lifestyle in children with ADPKD

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

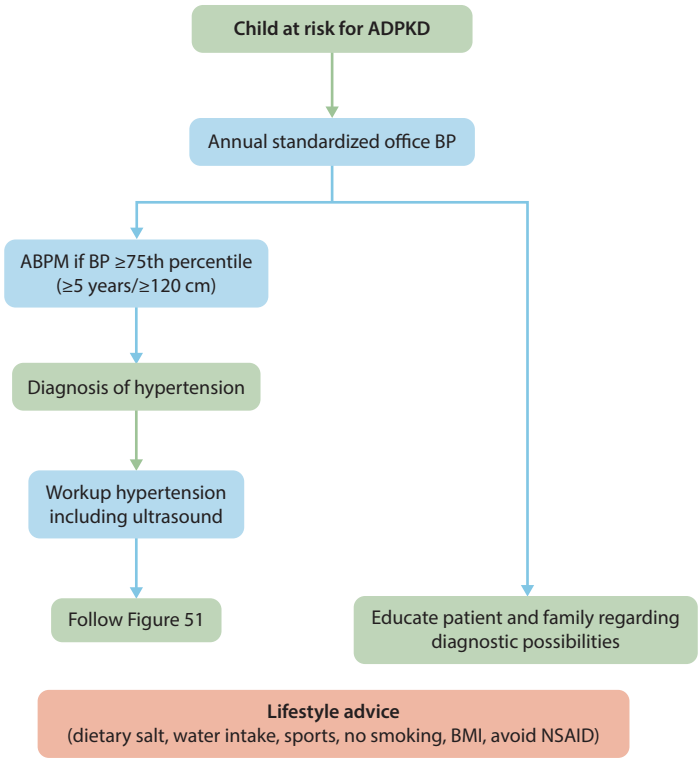


Figure 53 | Follow-up of children at risk for autosomal dominant polycystic kidney disease (ADPKD), which can be performed by a general practitioner, pediatrician, or pediatric nephrologist. ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; NSAID, nonsteroidal anti-inflammatory 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. Assessment for extrarenal manifestations should be recommended as stated in Chapter 6.

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).

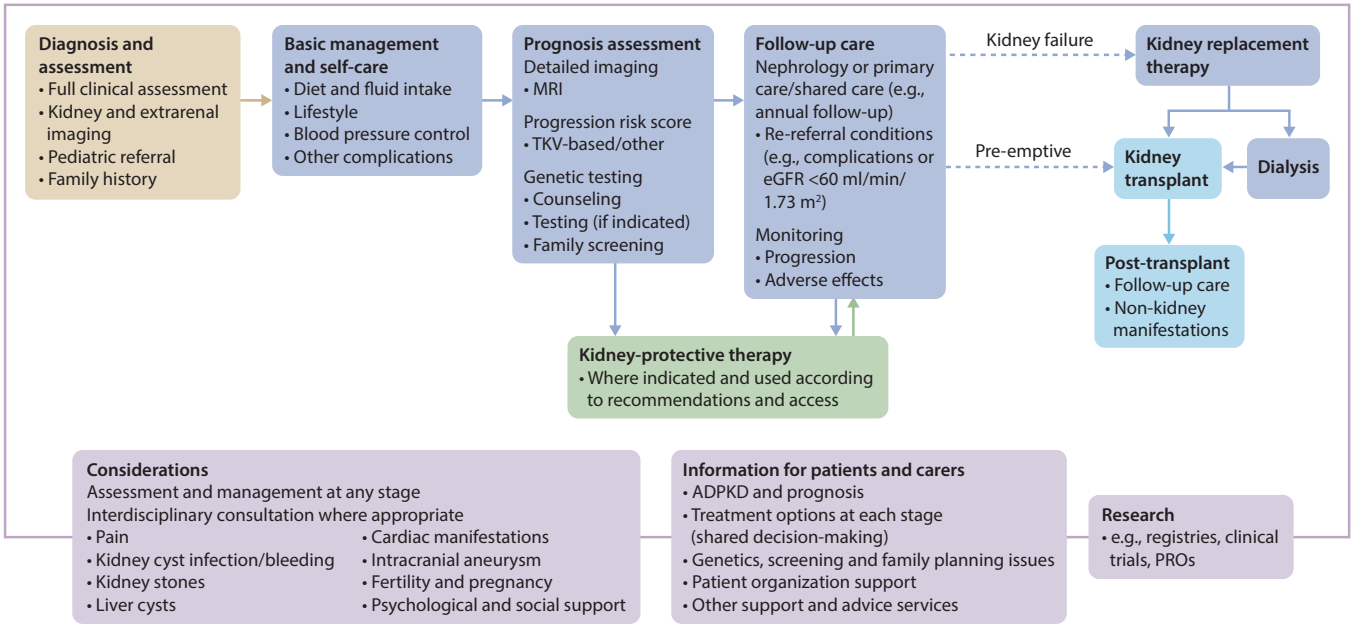


Figure 56 | A proposed autosomal dominant polycystic kidney disease (ADPKD) care pathway. Ultrasound-based kidney imaging, including kidney length measurements, could be considered if MRI or computed tomography is not routinely available. eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PROs, patient-reported outcomes; TKV, total kidney volume. Adapted from EAF Co-chairs *et al.*[766]; Mao *et al.*[874]; Ong *et al.*[875]

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

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

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 in registries that gather outcome data using standardized data definitions.**

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

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 that are caused by single pathogenic variants in one ADPKD gene (i.e., monoallelic), with autosomal dominant inheritance.[1–3] Thus, children and siblings of people with ADPKD are normally at a 50% risk of also having ADPKD. Multigenerational transmission is common, but apparent *de novo* pathogenic variants are implicated in approximately 20% of cases.[4] The major genes causing ADPKD are *PKD1* and *PKD2*, together accounting for >90% of affected families involved in research studies (Table 1).[5,6] However, several minor genes with an ADPKD spectrum phenotype have been described in the past decade, and these 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 associated genes being *PRKCSH* and *SEC63* (Table 2).[12–14] Single pathogenic variants among a few additional genes have been implicated in ADPLD,[15] and some of these can also result in an ADPKD phenotype (Table 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; Table 5).

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

To help navigate the complexity of cystic kidney and liver diseases caused by a single pathogenic variant, we propose the naming scheme shown in Tables 1 and 2. The proposed format is a descriptor of the disease followed by the name of the causal 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 for continued use of the disease name—ADPKD—that nephrologists, other healthcare providers, and affected people are familiar with and facilitates the identification of disease characteristics associated with the specific causal gene.

We have separated the genes causing ADPKD into different groups, as follows: major genes; minor genes with strong supporting data of pathogenicity; and suggested genes, for which supporting data are limited at this stage. We have put the major genes, *PKD1* and *PKD2*, into a separate group because they are the causative genes in the vast majority (>95%) of typical ADPKD cases with risk of kidney failure. We advise using the name ADPKD followed by the disease gene as the disease designation for the strongly supported minor genes (e.g., ADPKD-*ALG5*). We propose that this designation be used because this is the most likely diagnosis that people with pathogenic variants in these genes would receive based on imaging analysis alone (without genetic testing). The designation of ADPKD, without the name of the gene, can be applied to people with pathogenic variants to minor genes with limited evidence of pathogenicity only when the phenotype is consistent with ADPKD and no genetic or clinical data suggest a different form of cystic disease. The designation of ADPKD should be based on not only the finding of a likely pathogenic variant in a minor gene when a clinical diagnosis of ADPKD is uncertain. We understand that new ADPKD genes likely will be identified, and new evidence about pathogenicity of existing genes will be described, and so the gene classifications likely will change over time.

The disease designation of ADPLD-*PRKCSH* or ADPLD-*SEC63* is given to the major causes of ADPLD (Table 2). The sole minor gene that has been shown with definitive evidence to cause ADPLD—*GANAB*—is given a similar designation: ADPLD-*GANAB* (Table 2). For other genes suggested to be associated with ADPLD, only limited data support this possibility at this time, and the diagnosis of ADPLD should be made only when a phenotype consistent with ADPLD is present (Table 2).

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

We understand that the diagnosis of ADPKD is most often made on clinical, imaging, and family history grounds, not based on genetic testing, and we do not propose that genetic testing is necessary for everyone. Therefore, in the absence of genetic testing, a classical ADPKD spectrum phenotype of bilateral kidney cysts, enlarged kidneys, liver cysts, and possibly abnormal kidney function or kidney failure will continue to be termed ADPKD. Likewise, moderate-to-severe PLD with only very few or no kidney cysts will continue to be termed ADPLD, even in the absence of genetic testing. Specific gene names can be added after a genetic diagnosis is made.

Table 1 | Genes associated with the ADPKD spectrum, designations, and phenotype

Gene	Screened families, %	No. of families[b]	Disease designation	Kidney phenotype	Extrarenal phenotype	Comments
The major ADPKD genes and nomenclature for unknown, not screened, and unresolved typical cases						
Unknown/not screened/ unresolved			ADPKD	Bilateral PKD, kidney enlargement, age-related CKD, may result in KF	Liver cysts including severe PLD, increased risk of ICA	Wide phenotypic range in terms of TKV and KF risk and timing
PKD1	~48	>3250	Truncating pathogenic variant: ADPKD-*PKD1*	Bilateral PKD, early kidney enlargement, CKD G3, age ~40 yr, KF in 50s	Liver cysts including severe PLD, increased risk of ICA	Some disease variability, including a more benign course, sometimes associated with mosaicism
	~19	>1750	Nontruncating pathogenic variant: ADPKD-*PKD1*	Bilateral PKD, kidney enlargement, age-related CKD, may result in KF	Liver cysts including severe PLD, increased risk of ICA	Phenotype ranges from severe as *PKD1* truncating to mild PKD in old age, partly depending on the degree of residual protein function
PKD2	~15	>1000	ADPKD-*PKD2*	Bilateral PKD, milder and later kidney enlargement, CKD G3, age ~55 yr, KF in 70s	Liver cysts including severe PLD, increased risk of ICA	Some disease variability, including a more severe or more benign course
Minor ADPKD genes with definitive-to-moderate evidence of disease involvement[a]						
ALG5	<0.5	<10	ADPKD-*ALG5*	Mild to moderate cyst development with limited kidney enlargement and fibrosis; CKD and some KF in older adults[18]	A few liver cysts in a minority of people	
ALG9	<0.5	<20	ADPKD-*ALG9*	Mild to moderate cystic disease with significant CKD in older adults[9]	Liver cysts are common.	Biallelically, associated with the congenital disorder of glycosylation, type IL (CDG1L)
DNAJB11	<0.5	<30	ADPKD-*DNAJB11*	Bilateral small cysts, limited or no kidney enlargement, progressive fibrosis, limited CKD G3a <55 yr, but KF in 70s[8,19]	Liver cysts, usually mild. ICA and vascular risk are possible.	ADPKD-*DNAJB11* has similarities to ADTKD, because of the small, fibrotic kidneys, but visible cysts are usually present. Biallelically, associated with renal-hepatic-pancreatic dysplasia[20]
GANAB	<0.5	<20	ADPKD-*GANAB*	Mild cyst development, limited CKD, no KF[7]	Liver cysts, including severe PLD; ICA risk unclear	Can present as ADPLD
IFT140	1–2	<50	ADPKD-*IFT140*	Few, large bilateral cysts resulting in kidney enlargement with kidney function usually preserved into old age[21]	Liver cysts only rarely seen, with risk of ICA unclear	Biallelically, associated with short-rib thoracic dysplasia (SRTD9) and retinitis pigmentosa (RP80)
NEK8	<0.5	<20	ADPKD-*NEK8*	Bilateral PKD, kidney enlargement, KF in childhood, occasionally later in cases of specific alleles or mosaicism[22]	Liver cysts are rare.	*De novo* occurrence was reported in 75% of reported cases. Biallelically, associated with renal-hepatic-pancreatic dysplasia and nephronophthisis (NPHP9)
Suspected monoallelic PKD genes with limited evidence of disease involvement or not assessed[a]						
ALG6	<0.5	<10	ADPKD (only when the phenotype is consistent with this diagnosis)	Generally mild with or without persevered kidney function[23]	Liver cysts, including severe PLD	Can present with mainly a liver phenotype. Monoallelic *ALG6* is likely a lower-penetrant phenotype. Biallelically, associated with the congenital disorder of glycosylation, type IC (CDG1C)
ALG8	~1	<40[c]	ADPKD (only when the phenotype is consistent with this diagnosis)	Generally mild cystic kidney disease with preserved function into old age[24]	Liver cysts, including severe PLD; ICA risk unclear	Can present with mainly a liver phenotype. *ALG8* is likely a low-penetrant genotype.[24,25] Biallelically, associated with congenital disorder of glycosylation, type 1H (CDG1H)
PKHD1	~1	<50[c]		Generally, very mild cystic kidney development with preserved function into old age[26]	Liver cysts are common, and can be seen without kidney cysts.	Biallelic pathogenic variants are associated with ARPKD, which can present with mainly a liver phenotype. Monoallelic *PKHD1* is likely a low-penetrant genotype, including people with no cysts.[25]

AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CKD, chronic kidney disease; ICA, intracranial aneurysm; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; TKV, total kidney volume.

[a]Evaluation from ClinGen (https://search.clinicalgenome.org/kb/gene-validity?page=1&size=25&search=).

[b]Estimate of number of published families.

[c]Additional people with monoallelic loss-of-function variants have been identified but the kidney phenotype is unknown or nonpenetrant.

The major ADPKD genes are bolded. The chart has been divided into the major genes, the minor genes with a moderate level of evidence, and the possible minor genes with limited evidence. ADPKD is used as the disease designation of the major and well supported minor genes.

Table 2 | Genes associated with the ADPLD spectrum, designations, and phenotype

Gene	Screened families, %	No. of families[b]	Disease designation	Liver phenotype	Kidney phenotype	Comments
The major ADPLD genes and nomenclature for unknown and not screened typical cases						
Unknown/ Not screened/ Unresolved			ADPLD	Multiple liver cysts and often liver enlargement	None, or very few kidney cysts	Disease variability from few liver cysts to severe PLD
PRKCSH	~50	>70	ADPLD-*PRKCSH*	Multiple liver cysts and often liver enlargement[26]	None, or very few kidney cysts	Disease variability from few liver cysts to severe PLD
SEC63	~25	>60	ADPLD-*SEC63*	Multiple liver cysts and often liver enlargement[26]	None, or very few kidney cysts	Disease variability from few liver cysts to severe PLD[26]
Minor ADPLD genes with definitive evidence of disease involvement[a]						
GANAB	1–5	<10	ADPLD-*GANAB*	Multiple liver cysts and often liver enlargement, but liver cysts may not be present[7,15]	Kidney cyst number variable from none to multiple, including an ADPKD spectrum phenotype	Can present as ADPKD-*GANAB*
Suspected monoallelic PLD genes with limited evidence of disease involvement or not assessed[a]						
ALG6	<1	<10	ADPLD (only when the phenotype is consistent with this diagnosis)	Liver cysts including severe PLD[23]	Kidney cyst number variable from none to multiple	Can present with mainly a kidney phenotype. Monoallelic *ALG6* is likely a lower-penetrant phenotype. Biallelically, associated with the congenital disorder of glycosylation, type IC (CDG1C)
ALG8	1–5	<20[c]	ADPLD (only when the phenotype is consistent with this diagnosis)	Multiple liver cysts and often liver enlargement, but liver cysts may not be present[15]	Kidney cyst number variable from none to multiple, including an ADPKD spectrum phenotype	Can present with mainly a kidney phenotype. Monoallelic *ALG8* is likely a lower-penetrant phenotype. Biallelically, associated with the congenital disorder of glycosylation, type IH (CDG1H)
LRP5	<1	4		Multiple liver cysts and often liver enlargement[27]	None, or very few kidney cysts	Based on missense variants in 1 family and 3 people. Monoallelic *LRP5* variants are also associated with familial exudative vitreoretinopathy.
PKHD1	~1	<25[c]		Liver cysts are common and can be seen without kidney cysts. Not usually associated with severe PLD[15]	Generally, very mild cystic kidney development with preserved function into old age	Biallelic pathogenic variants are associated with ARPKD, which can present with mainly a kidney phenotype. Monoallelic *PKHD1* is likely a low-penetrant phenotype.
SEC61B	<1	2		Numerous small cysts[15]	Very few or none	Data based on 2 patients

ADPLD is used as the disease designation of the major and strongly supported minor genes. ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; ARPKD, autosomal recessive polycystic kidney disease; PLD, polycystic liver disease.
[a]Evaluation from ClinGen (https://search.clinicalgenome.org/kb/gene-validity?page=1&size=25&search=).
[b]Estimate of number of published families.
[c]Additional people with monoallelic loss-of-function variants have been identified but the liver phenotype is unknown or nonpenetrant.
The major genes are bolded. The chart has been divided into the major genes, the minor gene with definitive evidence, and the possible minor genes with limited evidence.

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

Genetic testing does not always identify a diagnosis. In a real-world clinical testing setting, the positive test rate is likely 75% at best and is lower in people with atypical disease.[25] Hence, in a substantial proportion of people, no likely pathogenic variants are identified, or only variants classed as being of uncertain significance (VUS), or variants in genes for which a causative association with monoallelic PKD has not yet been proven, 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 clinical diagnosis of ADPKD or ADPLD would remain. A diagnosis of ADPKD or ADPLD should not be based on the finding of a likely pathogenic variant in a gene for which a causative association with monoallelic PKD has not yet been proven, when a clinical diagnosis of ADPKD is uncertain.

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

The major genes for ADPKD are *PKD1* and *PKD2*, and people with variants classed as "pathogenic" or "likely pathogenic" will be referred to as having ADPKD-*PKD1* or ADPKD-*PKD2*, respectively (Table 1). The minor genes with strong-to-moderate support of pathogenicity that we also suggest including in the ADPKD group are *ALG5, ALG9, DNAJB11, GANAB, IFT140*, and *NEK8*, with the designations ADPKD-*ALG5*, etc., as listed in Table 1.[7–11,22,23] The minor ADPKD gene–associated diseases have distinctive phenotypes, but they overlap clinically with ADPKD-*PKD1* and ADPKD-*PKD2*. This disease-gene designation 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 an increased total kidney volume (TKV), due to a few large cysts, but a low risk of kidney failure (Table 1).[10] In contrast, ADPKD-*DNAJB11* typically is associated with development of only a few small cysts and with no increase in TKV, but the risk of kidney failure later in life, due to kidney fibrosis, is high.[8,19] Including the gene in the designation also serves to identify people with the minor genes for whom treatment with the presently approved drug for ADPKD (tolvaptan) is not known to be efficacious, as similar people were unlikely to have been included in the clinical trials given the recruitment criteria.[28,29] Use of cyst-number criteria for diagnosing or excluding ADPKD,[30,31] and use of the Mayo Imaging Classification (MIC) to define patient outcomes,[32] also should be limited to ADPKD-*PKD1* and ADPKD-*PKD2*. Given that ~25% of people with ADPKD are genetically unresolved by clinical testing, which often screens for atypical cases,[25] new genes likely will 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 tested, ADPLD will be employed as the disease name for the major ADPLD genes, *PRKCSH* and *SEC63*, and the minor gene when pathogenicity is well supported.

Variants in the major genes for ADPLD are *PRKCSH*[12,13,33] and *SEC63*,[14,15] and variants classified as "pathogenic" or "likely pathogenic" will be referred to as having ADPLD-*PRKCSH* and ADPLD-*SEC63*, respectively. The minor ADPLD gene with strong supporting data is *GANAB*, with the designation ADPLD-*GANAB*. For genes with limited evidence of pathogenicity, including *LRP5*,[34] *ALG6, ALG8, SEC61B,* and monoallelic *PKHD1*,[15] the ADPLD designation without the name of the gene should be used only when it is consistent with the phenotype. This usage could change if new evidence clearly links these genes to ADPLD, and if the supporting data were classified as at least "moderate" by ClinGen. New ADPLD genes likely will be identified and added to the current list of genes.

Although people with *GANAB* pathogenic variants often have an ADPLD phenotype, kidney cysts can be the predominant manifestation in some cases.[7,24,25] Therefore, a nomenclature such as, for instance, ADPKD-*GANAB* or ADPLD-*GANAB*, should be used, depending on whether the kidney disease or the liver disease predominates. Due to varied presentations associated with pathogenic variants to these genes, both ADPKD-*GANAB* and ADPLD-*GANAB* can be defined as being in the same family. If no genetic data are available, the ADPKD or ADPLD designation should be used based on the disease presentation. *GANAB* can be associated with severe, clinically significant PLD, similar to *PRKCSH* and *SEC63*. Both ADPKD-*PKD1* and ADPKD-*PKD2* can present with severe PLD, and especially for *PKD2*, the kidney disease can be very mild; therefore, these 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 the following: frameshifting deletions, duplications, or insertions; nonsense variants; canonical splicing variants; and large rearrangements (deletions, duplications, or insertions) involving ≥1 exon, termed copy number variants. Nontruncating pathogenic variants are defined as the following: small inframe deletions, duplications, or insertions; missense variants; and noncanonical splicing variants. Often, people with ADPKD-*PKD1* who have truncating variants have poorer kidney disease outcomes than do those with nontruncating variants.[35,36] Hence, although ADPKD-*PKD1* is usually associated with the most severe kidney disease, some nontruncating alleles can still generate a significant amount of functional protein (are partially penetrant or hypomorphic), and thus, they may be associated with less severe disease, including very mild PKD without risk of kidney failure.[37,38] Therefore, whether the *PKD1* variant is truncating or

nontruncating should be indicated in diagnostic reports. Nonetheless, a significant proportion of *PKD1* nontruncating alleles are likely fully inactive (no functional protein is generated from the pathogenic allele); *in silico* methods to differentiate alleles that are fully or partially penetrant are under development.[5] Some people with *PKD1* truncating variants can have milder kidney disease.[39] 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, specification of 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 person with ADPKD need to be educated about the significance of the ADPKD and ADPLD nomenclature.

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. Adding the gene name to the ADPKD disease name likely will result in a better appreciation of the expected phenotype and outcomes than a description of the disease as ADPKD alone. For example, people with ADPKD-*PKD1,* especially when it occurs with a truncating change, are at high risk for future kidney failure, and treatment options may be suitable. In contrast with the risk in the rarer ADPKD-*IFT140*, the chance of kidney failure is small. Therefore, since the risk of kidney failure in people with ADPKD-*IFT140* is much lower than that for those with truncating ADPKD-*PKD1*, this should be a consideration in determining insurance policies and coverage. Therefore, a partnership of the PKD community with PKD foundations and groups from around the world, to actively educate stakeholders, is important. Similar arguments can be made relating to 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.[40] Apart from a *PKD2* variant specific to Taiwan, ADPKD affects all populations, with no common pathogenic variant enriching the disease in a geographic area or racial and/or ethnic group.[41] Estimates of prevalence have varied more than 5-fold, especially between population and genetic studies. This variability likely is due at least partially to incomplete identification of all people with ADPKD in population studies given that the age-related phenotype often goes unrecognized in younger people. The discrepancy also is related to what is defined as ADPKD, especially for mild cases. Improved imaging indicates that having multiple cysts in the kidney (above the threshold in the Pei imaging diagnostic criteria[30,31]) is not a rare occurrence, and a significant proportion of the cases are of monogenic origin, such as those resulting from minor ADPKD genes or weakly penetrant alleles at the major genes.

A prevalence of 1 in 1000 is an often-quoted figure derived from the classic study by Dalgaard *et al.* of a population in Copenhagen, published in the 1950s.[42] The figures were not derived from point prevalence data; they are estimates of genetic prevalence of the disease at birth based on the theoretical risk of being ill from ADPKD during a lifetime of 80 years (8 per 10,000 people). Several more recent population studies have estimated the prevalence of ADPKD using various databases in Europe and the United States (U.S.; Supplementary Table S5[43–50]). Estimates from these studies vary somewhat, having a value of 3.96 per 10,000 in the European Union (EU) in 2012,[49] a value of between 2–4 per 10,000 in various studies in the US,[43,46–48] and a slightly higher level of 5.7 per 10,000 in the Seychelles. The prevalence seems to be higher in the populations of European ancestry, reflecting either a possible founder effect or an underserved Black population.[50] A recent Olmsted County study (1980–2016) of the Rochester Epidemiology Project database, and radiologic databases, found a prevalence of 6.8 per 10,000 for people with "definite" or "likely" cases of ADPKD.[46] This prevalence increased to 12.4 per 10,000 when people with "possible" ADPKD 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 per 10,000) with selection determined by the International Classification of Diseases (ICD) codes for ADPKD and confirmed clinically.[25]

Lanktree *et al.*[44] screened the sequenced "normal" populations (total >200,000) of the Genome Aggregation Database and Breast Cancer Risk and Various Outcomes study (BRAVO) for high-confidence pathogenic variants to *PKD1* and *PKD2* and determined a prevalence of ADPKD of 9.3 cases per 10,000 sequenced. This estimate likely reflects an undercounting of people with asymptomatic ADPKD in population studies, but it also may indicate that some proposed pathogenic variants do not result in clinically significant disease. Prevalence values for *PKD1* and *PKD2* pathogenic variants were 6.8 and 2.6 per 10,000, respectively, resulting in a ratio of *PKD1*/*PKD2* of 2.6. This prevalence is much lower than the >4 found in kidney clinic populations, probably reflecting the milder phenotype associated with *PKD2* variants (people with *PKD1* pathogenic variants also may be underrepresented in these "normal" populations). Following whole-exome sequencing (WES) of the Geisinger population,[25] a possible genetic cause was found in 180 of 235 people with ADPKD (76.6%). The majority had rare variants to *PKD1* ($n = 127$) or *PKD2* ($n = 34$), whereas 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 of 54 (77.8%) and 17 of 24 (70.8%) people with such a variant, respectively, being ICD-coded as ADPKD. This level was much lower for *IFT140* (2.5%), *GANAB* (7.1%), and (the non-ADPKD-defined gene) *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 the level at which high-confidence pathogenic variants to the various ADPKD genes result in clinically significant cystic outcomes remains to be seen.

1.2.1 Prevalence of ADPKD in kidney failure populations

ADPKD is an important cause of kidney failure. In the U.S. in 2020, the number of people defined as having cystic kidneys and starting kidney replacement therapy (KRT) was 3396, representing an incidence of 2.60% of the KRT population total.[51] Not surprisingly, given the inheritance pattern, more people with PKD were receiving nephrology care ≥12 months before kidney failure than any other kidney-failure group (55.6%); however, only 34.8% started receiving nephrology care <1 year before kidney failure. In 2020, the number of people with cystic kidneys receiving KRT in the U.S. was 40,968 (i.e., a prevalence of 5.07% of the KRT total). This represents 115 per million people in the U.S.. Of these, 63% had a kidney transplant, 29% were receiving hemodialysis (HD), and 8% were receiving peritoneal dialysis (PD).

In the European population collected in the European Renal Association (ERA) Registry in 2020,[52] the prevalence of polycystic kidneys, ADPKD type, was 137 per million, representing 5% of the KRT population. In the <65-year age group, 9% of the KRT population had PKD, with 55% of those with PKD in the age range of 45–64 years. In this PKD KRT population, 67% had a kidney transplant, 30% were receiving HD, and 3% were receiving PD.

1.3 Diagnosis

Obtaining a firm diagnosis in ADPKD is a first step toward receiving appropriate care, and when possible, starting treatment. Traditionally, ADPKD has been diagnosed in at-risk family members (children, siblings, or occasionally a parent) of an affected individual, using abdominal imaging (Figure 1). We continue to recommend imaging as an initial diagnostic tool. However, genetic testing has become widely available in many countries and is increasingly employed in ADPKD families. In ADPKD families that already have a genetic diagnosis, allele-specific testing for the family variant may be the easiest diagnostic method (Figure 1). How to obtain a firm diagnosis when kidney cysts are detected incidentally by imaging is described in Figure 2.

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

Decisions about whether to undergo testing for ADPKD by abdominal imaging or genetic screening should take into account the wishes of people with ADPKD and their families. To ensure that informed decisions are made, before testing, healthcare providers should explain the benefits and harms of the testing (Table 3) and articulate the appropriate methods. Reasons for taking the tests vary, depending on the circumstances of the individual people and their families. ADPKD most often can be diagnosed in people determined to be at risk using abdominal imaging, but genetic testing can be helpful in certain situations.[30,53] Questions related to diagnosing ADPKD in children are discussed in Chapter 9.

Table 3 outlines factors to consider when screening people who are at risk for ADPKD, using genetics and/or imaging. Although strong evidence indicates that testing to obtain a genetic diagnosis can be of value to at-risk persons and their families,[54] well-documented potential complications also need to be considered when discussing options (Table 3).[30,53,55,56] Opinions regarding testing people who are at risk, including those regarding when and how to test, can vary among individual people, families, and cultures (see also Chapter 10). These values and preferences, plus the availability of specific modalities for testing, need to be taken into consideration when counseling people about testing options and likely outcomes, and when explaining results. The availability of specific tests, whether imaging or genetic, varies greatly among centers and 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 are the possible out-of-pocket costs of testing, which need to be explained carefully.

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

In many circumstances, a nephrologist (playing a leading role) and a genetic counselor experienced in ADPKD can provide pretest and posttest counseling to the person who is at risk, order the appropriate tests, and interpret the data associated with diagnosing ADPKD. However, in more complex cases, the involvement of a multidisciplinary team is advised. For genetic testing, this involvement may include adding a medical geneticist experienced in ADPKD to the team, to interpret complex genetic results.[55] For follow-up radiologic screening, a radiologist skilled in ADPKD should be involved. A team-based approach can provide counseling to the individual person and family, arrange sample collection, order tests, interpret results, return results to patients with appropriate counseling and make recommendations for follow-on evaluations.[57–60] A counseling checklist can help the nephrology team describe the benefits and limitations of the various 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 also can be utilized by patients' primary provider. Patients should be able to contact their primary provider, usually the nephrologist, so that questions can be answered throughout the process.

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

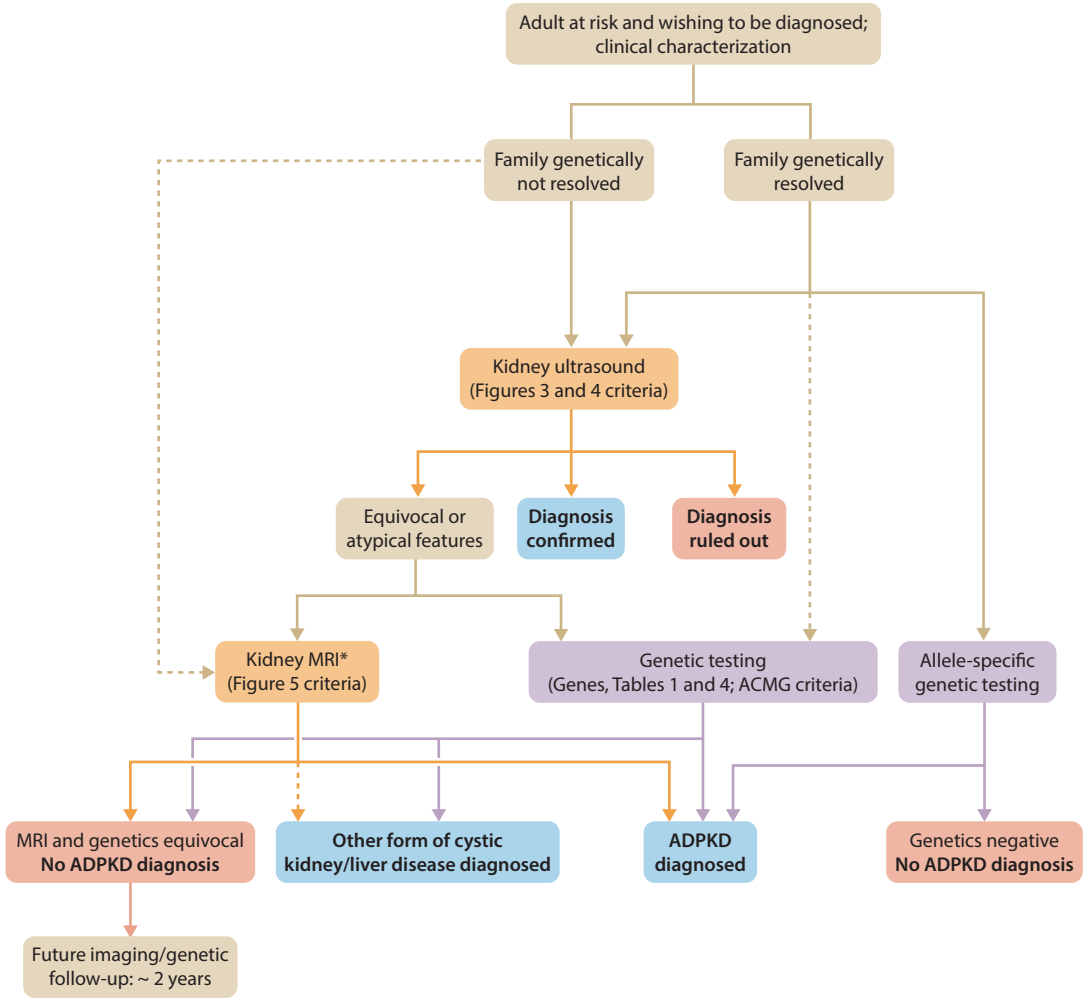


Figure 1 | Diagnosis algorithm in at-risk adults (positive family history) for autosomal dominant polycystic kidney disease (ADPKD). ACMG, American College of Medical Genetics and Genomics; MRI, magnetic resonance imaging. *Computed tomography, either with or without contrast, can also be used. Abdominal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

Counseling should be provided by a nephrologist, a genetic counselor, or other medical professional with expertise in ADPKD, 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 approach is important not only when the results are positive, but also when the imaging or genetic results are equivocal and follow-up analyses are required. As indicated, a team-based approach to ordering testing is recommended. Healthcare providers should initiate testing only 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: For screening adults at risk of ADPKD, we recommend first using abdominal imaging by ultrasound, in the context of the family history, kidney function, and comorbidities (*1B*).

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

Recommendation 1.3.1 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. Moderate evidence supports this recommendation.

Key information

Balance of benefits and harms. Obtaining a diagnosis of ADPKD is key to being referred to a nephrologist experienced in managing ADPKD who can oversee care and ensure that clinical manifestations of the disease, such as early-onset hypertension, are monitored and treated appropriately. We recommend using abdominal imaging performed by ultrasound to initially diagnose ADPKD in people at risk

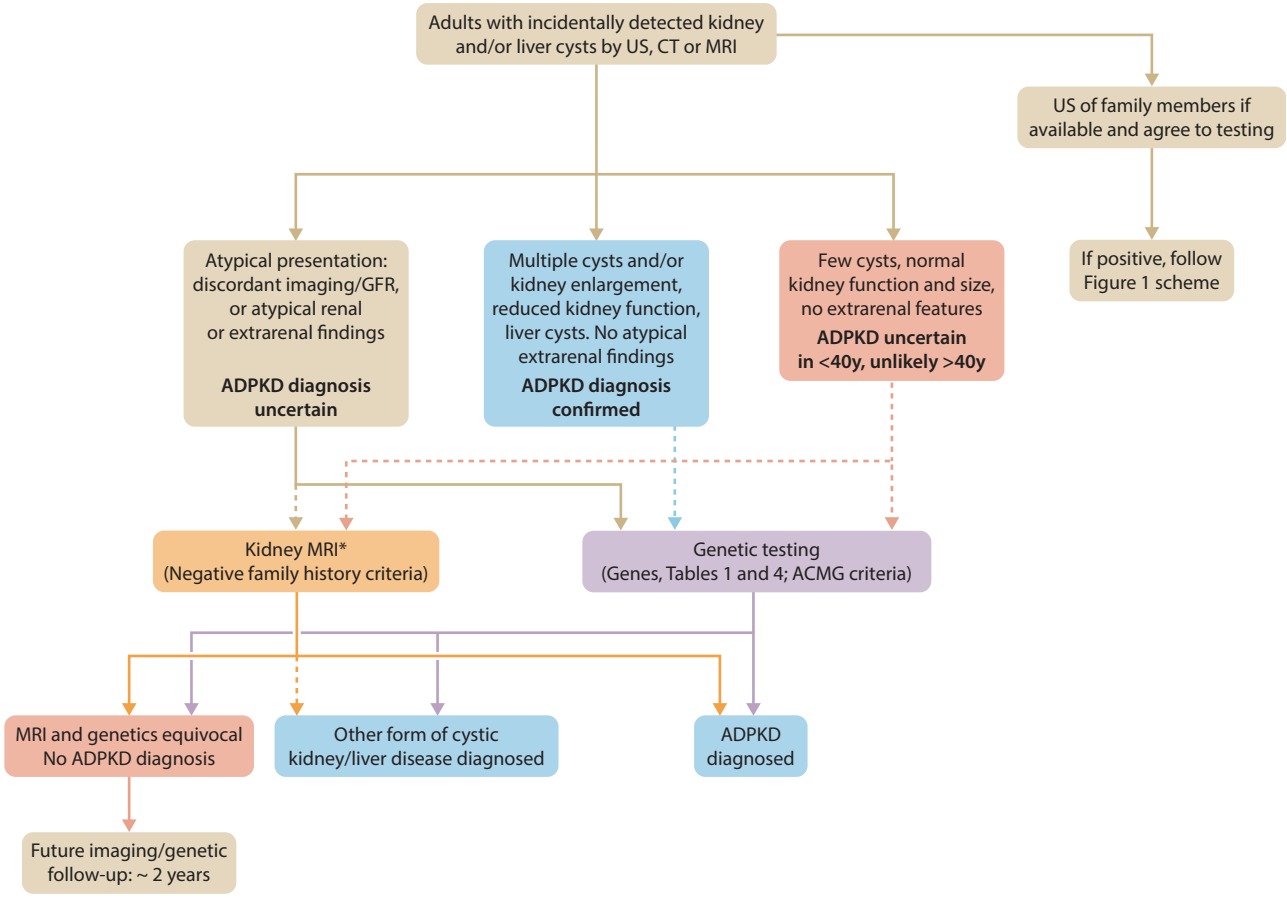


Figure 2 | Diagnosis algorithm in adults with incidentally detected kidney and/or liver cysts in absence of known family history of autosomal dominant polycystic kidney disease (ADPKD). Solid lines indicate tests that are suggested, and dashed lines indicate tests to consider. *CT with or without contrast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

(Figure 1). Being at risk means having an affected family member, most often a parent. Ultrasound is noninvasive, generally available, and inexpensive. In situations in which 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 they are generally very safe, but CT employs ionizing radiation. The use of intravenous (i.v.) contrast to obtain maximal resolution to see small cysts using CT can be a risk in people with abnormal kidney function. For MRI, contraindications include the presence of certain implanted devices or retained metal, and patient discomfort inside the magnet. Genetic testing also can clarify a diagnosis (Practice Point 1.3.8).[61]

Although the accuracy of different imaging modalities was not systematically reviewed, strong evidence indicates that imaging is a reliable means to diagnose or exclude ADPKD in the context of a positive family history.[30] Ultrasound is recommended as the first method of evaluation. Specific cyst number and age criteria have been defined for identifying or excluding ADPKD (Figures 3 and 4).[30] These criteria are generally reliable, but apply only to typical ADPKD, meaning known ADPKD-*PKD1*, and ADPKD-*PKD2*, although they may not apply to those with occasional hypomorphic pathogenic variants at these loci. Similarly, cyst number and age criteria for diagnosis or exclusion have been described for MRI in people with ADPKD-*PKD1* and ADPKD-*PKD2* and a positive family history.[31] Similar CT data have not been published, but the cyst numbers per age for the 97.5th-percentile for the general population are available.[62] Using imaging to diagnose ADPKD in people with an unknown family history is discussed in Practice Point 1.3.7. In people with equivocal and atypical imaging results, genetic analysis can be helpful. In genetically resolved families, genetic testing of at-risk family members can rapidly and definitively provide a diagnosis (Figure 1; Practice Point 1.3.9).

Certainty of evidence. The certainty of evidence was graded as moderate. Performing clinical trials to determine the best means to diagnose ADPKD is not practical, but several studies involving affected and control populations have been performed to develop cyst-number criteria for diagnosing or excluding ADPKD. Initial ultrasound criteria for ADPKD-

Table 3 | Factors to consider when testing (by imaging and/or genetics) people at risk for ADPKD

Possible value of early screening	Possible complications of early screening
• **Resolve diagnosis odyssey.** The individual person and family may obtain a definite diagnosis.	• **Psychological 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). It is especially disconcerting if there is no family history of ADPKD.
• **Ability to manage and treat ADPKD.** Appropriate management and treatment of the affected person can be initiated.	• **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.
• **Initiate screening for extrarenal manifestations.**	• **High cost.** Some testing, including genetic testing and certain types of imaging, may not be fully covered by insurance or government-funded health plans.
• **Enable enrollment in clinical trials.**	• **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.
• **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.	• **Specialist knowledge to interpret test results may not always be available.** The supply of professionals with genetics expertise for kidney diseases is limited.
• **Appropriate family planning.** Knowledge about the genetic nature of ADPKD might aid decision-making concerning care of the person and family planning.	
• **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.	

ADPKD, autosomal dominant polycystic kidney disease.

PKD1 were established in 1994,[63] and they were updated to the established unified criteria for ultrasonographic diagnosis of ADPKD based on analysis of ADPKD-*PKD1* and ADPKD-*PKD2* populations.[30] Overall, these criteria still are considered to be reliable, supporting this recommendation, but the criteria defined for ADPKD-*PKD2* had reduced sensitivity compared with those for ADPKD-*PKD1* due to a higher number of false negatives. The subsequent identification and characterization of additional ADPKD genes and *PKD1* hypomorphic alleles mean that these criteria may not be used universally. Using MRI to quantify the number of cysts for diagnosis or exclusion has been established in an ADPKD-*PKD1* and ADPKD-*PKD2* population.[31] These numbers also have been considered reliable, with the minor gene and hypomorphic variant provisions indicated above. Identification of a variant labelled "pathogenic" or "likely pathogenic" in a known ADPKD gene is diagnostic, but genetic testing does not always provide a definite answer.

Values and preferences. Several issues should be considered by people with ADPKD and their healthcare providers when selecting an imaging method. These include the availability and costs of imaging methods, which differ greatly in

Ultrasound criteria by age group to ***diagnose*** ADPKD when there is a positive family history							
Age (years)	Number of cysts (test criterion based on number of cysts)	ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown gene type	
		Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive test (%)	Sn (%)
15–29	≥3 total	100	94	100	70	100	82
30–39	≥3 total	100	97	100	95	100	96
40–59	≥2 in each kidney	100	93	100	89	100	90
60+	≥4 in each kidney	100	100	100	100	ND	ND

Figure 3 | Ultrasound criteria by age group to diagnose autosomal dominant polycystic kidney disease (ADPKD) in people with a positive family history based on a positive predictive value of the test.[30] The sensitivity (Sn) of a test is its ability to designate an individual with the disease as positive. ND, not determined; PKD, polycystic kidney disease.

Ultrasound criteria by age group to ***exclude*** ADPKD when there is a positive family history							
Age (years)	Number of cysts (test criterion based on number of cysts)	ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown gene type	
		Predictive value based on a negative test (%)	Sp (%)	Predictive value based on a negative test (%)	Sp (%)	Predictive value based on a negative test (%)	Sp (%)
15–29	≥1 total	99	98	84	97	91	97
30–39	≥1 total	100	96	97	94	98	95
40–59	≥2 total	100	98	100	98	100	98

Figure 4| Ultrasound criteria by age group to exclude autosomal dominant polycystic kidney disease (ADPKD) in people with a positive family history based on a negative predictive value of the test.[30] The specificity (Sp) of a test is its ability to designate an individual who does not have the disease as negative. PKD, polycystic kidney disease.

different parts of the world, not only between settings with high versus low levels of resources, but also among high-resource settings. Other factors to consider are the resolution needed, such as in cases when only small cysts are identified and potential adverse effects are possible, such as frequent radiation exposure with CT. 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 evaluating a person at risk for ADPKD, as it is inexpensive, portable, widely available, and does not require contrast or ionizing radiation. However, ultrasound does not offer high enough sensitivity for detecting very small cysts and therefore is not able to rule out ADPKD, especially in young people (aged <30 years). The low sensitivity level is a particular issue for evaluating potential kidney donors. Although technology has improved over recent decades, with new-generation ultrasound machines reliably detecting cysts of ∼5 mm, its availability is limited. Ultrasound sensitivity also can be reduced with large body habitus. At-risk young adults should undergo MRI if the ultrasound results are equivocal, as MRI offers superior sensitivity for very small cysts. MRI can detect cysts ≥2 mm in size, and the soft-tissue contrast is superior to that shown with ultrasound or CT. With CT, sensitivity for kidney cysts down to 2 mm is high when i.v. contrast is administered. CT can be useful if other concurrent pathologies are suspected, such as stone disease, solid kidney mass, kidney hemorrhage, or hydronephrosis. Genetic testing also can clarify a diagnosis, but it is not available in all parts of the world.

Resource use and costs. Ultrasound, the recommended first test to be used in screening a person who is at risk of ADPKD, is the least costly of the discussed modalities (ultrasound, CT, MRI) and the one most widely available. The availability and the cost of MRI and CT vary substantially among geographic locations, even among institutions within the same country. Therefore, when ordering an imaging examination, the radiologist providing the care needs to take these factors into consideration, along with the resolution of imaging needed in consultation with the person at risk. The availability and costs of genetic testing also vary widely across the globe. Of particular importance is informing individuals about the possible out-of-pocket expenses not covered by insurance.

Considerations for implementation. The availability of the different imaging modalities is an important consideration when determining how to diagnose ADPKD. Although in high-resource settings, ultrasound, MRI, and CT often are all available, in low- and middle-resource settings, 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 with MRI or CT, depending on the considerations given above. In countries where the cost of an MRI is similar to that of an ultrasound and MRI is readily available, MRI is an excellent alternative for the screening of people at risk for ADPKD. Genetic testing, when available, can clarify the diagnosis.

Rationale

For at-risk adults, obtaining a firm diagnosis of ADPKD is important, and it is the first step toward receiving appropriate care and treatment. As shown in Figure 1, the Work Group recommends using kidney imaging as the first means to diagnose ADPKD in those at risk (i.e., those with a positive family history [parent, sibling, and/or occasionally a child] of diagnosis with ADPKD). Using ultrasound as the first screening method and employing the described number-of-cysts-per-age criteria, to determine if a person is affected, are generally reliable methods (Figure 3). Having bilateral cystic disease, and a cyst number well above the diagnostic criteria means a that a positive diagnosis is made for ADPKD. Additional imaging or genetic testing is indicated primarily for providing prognostic information. If no cysts or very few cysts (considering age) are found, ADPKD usually can be excluded through employing the imaging criteria (Figure 4). If the imaging presentation is atypical, such as unilateral, asymmetric, or when a few cysts account for a large part of the increased TKV, or if additional clinical features suggest a differential diagnosis, additional imaging, and genetic testing can be helpful. In people in whom only a few cysts are found,

and the diagnosis is unclear, MRI or contrast-enhanced CT may be more definitive as they have greater sensitivity in identifying small cysts. Genetic testing also may be helpful in clarifying the diagnosis of ADPKD. The presentation of the disease in the family also should be considered when interpreting the imaging data in a person who is at risk.

Incidental discovery of cysts in a person without a known family history of ADPKD is not unusual, especially with the increasing utilization of imaging for abdominal indications (Figure 2).[64] Imaging of family members (such as parents) can be helpful to determine if cystic disease is present in the family. If a person is positive, follow-up can then proceed as outlined in Figure 1. 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 kidney cystic disease, a diagnosis of ADPKD usually can be made, although additional imaging and genetic testing can better define the disease. Imaging and genetic analysis of parents, siblings, and/or adult children also may 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 abnormality of kidney function at a level greater than that 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 can be helpful in obtaining 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 it may identify other disease manifestations, such as severe PLD.

Practice Point 1.3.5: For people with a positive family history of ADPKD, age-specific numbers of cysts seen on ultrasound have been described to diagnose or exclude ADPKD (Figures 3 and 4).

Cyst-number and age-range data for the diagnosis and exclusion of ADPKD using ultrasound have been determined from an analysis of 577 people with ADPKD-*PKD1* and 371 ADPKD-*PKD2*.[30] Simplified versions of these data are shown in Figures 3 and 4. For a positive diagnosis, the positive predictive value (PPV) is 100% for people with ADPKD-*PKD1* and ADPKD-*PKD2,* based on the defined number of cysts per age category, but the sensitivity level is lower, especially in younger people with ADPKD-*PKD2*, suggesting that follow-up imaging with a more sensitive method and/or genetic testing may be helpful in people aged <30 years (Figure 3). For people with an unknown gene type (for whom 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 aged >40 years with a family history of ADPKD-*PKD1* and ADPKD-*PKD2,* but it is lower for people with a family history of PKD2 and aged <30 years. For the age groups 15–29 years, and 30–49 years, a kidney ultrasound without any cyst detection is adopted as a criterion to exclude ADPKD. For the age group 40–59 years, a kidney ultrasound with only a single cyst is adopted as a criterion to exclude ADPKD. The specificity level is high across all age ranges and genotypes (Figure 4). For people with an unknown gene type (for whom genetic testing has not been performed), the NPV for ultrasound criteria is 91% for those aged 15–29 years and higher for those who are older. As most of the other genetic forms of ADPKD create milder disease than even ADPKD-*PKD2*, the exclusion criteria are not reliable for the minor genes.[7–11] Also, these criteria may not be reliable for weak hypomorphic alleles of the major genes.[6]

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

As for ultrasound, analysis of a population of 126 people at risk, plus 45 unaffected controls, has defined cyst-number criteria to be used with MRI for people aged 16–40 years. From this study, a number of cysts >10 was adopted as the criterion for diagnosing ADPKD, and a number <5 cysts was adopted for excluding the disease across the whole age range. This study analyzed only people with ADPKD-*PKD1* and

Magnetic resonance imaging (MRI) criteria for ages 16-40 years in people with a positive family history					
Age (years)	Number of cysts (test criterion based on number of cysts)	Predictive value based on a positive test (%)	Sensitivity (%)	Predictive value based on a negative test (%)	Specificity (%)
16–29	≥10 cysts	100	100		
30–40		100	100		
16–29	≥5 cysts			100	98.3
30–40				100	100

Figure 5 | Magnetic resonance imaging (MRI) criteria for ages 16–40 years in people with a positive family history.[31] The sensitivity of a test is its ability to designate an individual with the disease as positive. The specificity of a test is its ability to designate an individual who does not have the disease as negative.

ADPKD-*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 unavailable. Of note, the exclusion level of <10 cysts was suggested because one person in an ADPKD-*PKD2* family without the pathogenic variant had 10 cysts; but given that 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, use of a more conservative level of <5 cysts is suggested here, and an age >20 years.

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

Figure 2 describes the algorithm to follow when cysts are discovered incidentally by kidney imaging. Abdominal imaging should be considered for consenting parents, siblings, and/or adult children; and if a positive family history is found, the scheme as indicated in Figure 1 should be followed. If multiple bilateral cysts are identified with increased kidney volume, with or without liver cysts, and no other disease features are suggestive of a different cause of kidney cysts, the presumptive diagnosis is ADPKD. If the incidental diagnosis of kidney cysts was made by ultrasound, follow-up imaging by MRI or CT, and genetic testing, should be considered to confirm the diagnosis and 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 2).

If only a few incidental cysts are identified without kidney enlargement or liver cysts, no clear cutoff has been established for the number of kidney cysts required to make a diagnosis. However, analyses of unaffected people in the populations screened to establish the ADPKD imaging guidelines,[30,31] and of large populations in which 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 2012 potential kidney donors, 39% in the age range of 19–49 years had at least one cyst of size ≥2 mm, and this prevalence increased to 63% for people 50–75 years.[62] The 97.5th percentile for number of total cysts ≥5 mm was 10 for men and 4 for women aged 60–69 years; the >97.5th-percentile group is made up of those for whom an underlying genetic cause is suspected. Therefore, in people with a limited number of cysts and no increase or a 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 can clarify the diagnosis.

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

Increasingly, genetic testing is being employed to provide a firm diagnosis and prognostic information in cases of ADPKD (Section 1.4). However, making a diagnosis using genetics is not necessary in people with a typical presentation with large and diffusely cystic kidneys without extrarenal manifestations suggestive of a different disease. Nevertheless, even in typical ADPKD, genetic testing can provide a definite diagnosis, can help with determining the prognosis, and can enable a diagnosis in other family members.[61] Genetic testing also is 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 an indication that the person does not have ADPKD, and management, treatment options, and enrollment in clinical trials should not be changed based on the lack of a genetic diagnosis.

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

We advise use of targeted next-generation sequencing (tNGS) or whole-exome sequencing (WES), with an initiation analysis focus on PKD-related genes, for screening of people with suspected ADPKD. However, once a causal variant is defined within a family, Sanger analysis of just the pathogenic variant usually is sufficient to determine whether at-risk family members are affected (employing a long-range polymerase chain reaction approach for *PKD1*; Figure 1); thus, obtaining additional diagnoses within genetically characterized families can be performed rapidly and is relatively inexpensive. As an exception, the normal primary NGS screening should be performed for people with a phenotype that is very different than that seen in their family, such as having a limited number of cysts in a family with typical ADPKD and kidney failure.

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

Although genetic screening is not required for people with typical ADPKD to obtain a diagnosis, it can provide prognostic information. Specific situations in which genetic testing can be central to obtaining a clear diagnosis include those involving either unusually mild or severe disease, people with a negative family history and/or atypical imaging findings, or the presence of significant disease variability among family members, suggesting genetic complexity (Table 4).

As broad genetic testing becomes more prevalent, an incidental finding of a pathogenic variant suggesting ADPKD is becoming more common.[25] 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

Table 4 | Situations in which genetic testing can clarify the diagnosis and aid in determining a prognosis

Situation	Genetic findings
Limited number of cysts	Positive result can show a genetic origin (minor gene or hypomorphic allele).
Variable disease severity in a family	Mosaicism or biallelic/digenic disease can explain some extreme variability.
Atypical findings with imaging, such as asymmetric or unilateral disease	Positive result can show a genetic origin (including mosaicism or minor gene involvement).
Discordance between structural (MIC) and functional (GFR) ADPKD severity[a]	Genetic testing may reveal an atypical form of the disease or additional genetic or contributory factors, but nongenetic factors may also be important.
Negative family history	Positive result can show a genetic origin (*de novo* mutation can be proven).
Very-early-onset (VEO) ADPKD	Biallelic disease may be found (Chapter 9).
Related living transplant donor (aged <30 yr, especially if a few cysts detected)	Genetic testing can exclude the familial variant, if known, and test for other genetic causes.
Family planning and preimplantation genetic diagnosis (PGD)	Obtaining a genetic diagnosis can aid in family planning and enable PGD (Chapter 8).
All people	Genetic testing can confirm the diagnosis, identify the responsible gene and variant, and provide prognostic information.

ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; MIC, Mayo Imaging Classification (see definition in Chapter 9); PGD, preimplantation genetic diagnosis.
[a]Discordance may be reduced GFR without significant kidney enlargement, or an older adult with large kidneys but normal GFR.
For more information about mosaicism, and biallelic and digenic inheritance, see Practice Point 1.3.12.

determine if it occurred *de novo*, and to test for possible mosaicism, is indicated. People with *de novo* disease require specific psychological support because of the unexpected diagnosis. Variants in minor genes associated with ADPKD can have reduced penetrance so loss-of-function variants may not always result in cyst development.[24,25] Without cyst development, a diagnosis of ADPKD should not be given. Also, given the mild phenotype associated with single pathogenic variants of some of the minor genes, the finding of such discordance in a person with typical ADPKD should call into question whether the real (entire) cause of the PKD has been discovered and should indicate the need for additional testing.

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

In some situations, a definite exclusion diagnosis of ADPKD is required to make clinical decisions, such as for living, related donor candidates. If the potential donor is aged >40 years, 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 indicate an equivocal number of cysts and/or the age of the person is <30 years, genetic testing can determine if the potential donor has the familial pathogenic variant in genetically resolved families. Note that an affected family member should be tested first, and then information about the familial variant should be employed to perform targeted testing (cascade testing) on the asymptomatic living donor candidate.[65] In the scenario of just a few cysts being identified in the potential donor, 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 screen for all known genetic forms of PKD. Cysts also may be detected by imaging of a prospective donor with no known family history of PKD; in this case, broad genetic testing is helpful to determine the etiology of the cysts (Figure 2).

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

In situations of marked intrafamilial kidney disease variability, or if a *de novo* pathogenic variant is suspected, genetic testing can reveal complexity that explains the presentations (Table 4). Normally, one pathogenic variant to an ADPKD gene with dominant transmission is sufficient to cause ADPKD. Although being biallelic for fully penetrant pathogenic variants to *PKD1* or *PKD2* is not thought to be compatible with delivery of a live birth,[66] occasionally, in a family, more than one variant has a pathogenic role. One example is biallelic disease, in which at least one of the variants is hypomorphic, and the pathogenic changes are inherited from the 2 different parents.[38] An indication of biallelic disease is VEO-ADPKD (evident *in utero* or in infancy), but in cases in which typical ADPKD is seen in the parental generation and often elsewhere in the family (Chapter 9).[38,67–70] Sometimes, VEO-ADPKD cases with 2 hypomorphic alleles can have an apparent negative family history (mimicking ARPKD) because either of the single hypomorphic alleles alone (as found in the parents) result in either no or very mild cyst development (imaging of the parents with MRI or CT is suggested to detect mild disease).[67] Biallelic inheritance also can result in typical, adult-onset disease, with an indication of this inheritance being an apparent negative family history and/or marked differences in severity among family members (members with 1 or 2 pathogenic alleles).[38] Care should be taken to not exclude some more common hypomorphic variants.[71] Digenic disease, in which both a *PKD1* and a *PKD2* pathogenic allele are present, has been described only rarely.[72–74] Digenic disease is indicated when more than the expected 50% of family members are affected and/or when significant differences are present in disease severity among family members (those with 1 or 2 genes affected).

Approximately 20% of families with ADPKD are found to have *de novo* mutation.[4,75] Normally, these new mutations

occur in the development of the germ cells (eggs or sperm), and so the offspring derived from these cells 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, some with and some without the pathogenic variant. The number of cells with the pathogenic variant can range from <1% to ~50%, depending on when the mutation occurred, and levels of expression of the pathogenic variant in different organs. An indication of mosaicism is marked phenotypic variability among affected people in different generations in a family that appears to have a *de novo* mutation in the parental generation or among genetically resolved families with milder disease than that expected for the gene and/or variant type. A recent study of 20 ADPKD families with mosaicism showed that all had ADPKD-*PKD1*. Five families transmitted the variant to the next generation (i.e., the pathogenic gene variant also was present in the person's germ cells), and the other 15 were sporadic cases.[76] Overall, the disease was milder in the cases with mosaicism than in those in their offspring or people with a similar pathogenic variant, but the phenotype varied widely. In cases of mosaicism, next-generation sequencing methods are necessary to detect and quantify the number of cells with the pathogenic variant. Low-level mosaicism may not be detected by genetic testing, and so the solve rate of genetic testing in affected people with a negative family history is likely lower than that in those with an affected parent. 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.[77] Although the probability of this possibility occurring is low, it should be considered when counseling a sibling of an affected person with unaffected parents.

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

Some known or proposed ADPKD genes also are associated with recessive diseases (Table 1). Therefore, finding a pathogenic variant in such a gene means that the person is a carrier with the potential to have a child with the recessive disorder. This possibility is particularly significant for *PKHD1,* for which the carrier frequency is ~1 in 70, but it also could be important for some genes that are recessively associated with congenital disorders of glycosylation (CDGs; Tables 1 and 2).

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

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 (Table 5). *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),[78,79] but they normally can be differentiated from ADPKD by the range of pleotropic, extrarenal phenotypes and recessive inheritance. For the X-linked ciliopathy gene, *OFD1*, a pathogenic variant in female patients can result in a kidney phenotype closely mimicking ADPKD, but oral, facial, and/or digital abnormalities usually also are present (Table 5).[80] Hepatocyte nuclear factor-1 beta (HNF1B) is a transcription factor regulating the expression of many PKD genes, and monoallelic variants to *HNF1B* occasionally can be mistaken for ADPKD, but a range of other kidney, urinary tract, and other abnormalities most often also are present.[81] In addition, kidney cysts are part of Alagille syndrome.[82] Recessively inherited ARPKD is usually a much more severe disease than ADPKD, with congenital hepatic fibrosis rather than liver cysts, but adult presentations of ARPKD-*PKHD1* and biallelic-*PKD1* (ARPKD-*PKD1*) or -*PKD2* (ARPKD-*PKD2*) can result in confusion between the disorders.[83,84] 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], and hereditary leiomyomatosis and renal cell cancer [HLRCC]) can have kidney cysts as part of their phenotype.[85–89] Large deletions disrupting the adjacent *PKD1* and *TSC2* genes, the *PKD1/TSC2* CGS, often are associated with VEO-ADPKD and early kidney failure, but the TSC tumorous phenotype usually differentiates the diseases.[90,91] Single pathogenic variants in the collagen genes *COL4A3*, *COL4A4,* and *COL4A5* in females, can result in mild *COL4A*-related disease phenotypes, where kidney cysts can be present.[92–94] Gene defects associated with kidney stones also sometimes can result in a small number of kidney cysts. Finally, ADTKD, characterized by small fibrotic kidneys, occasional cysts, and kidney failure, has similarities to ADPKD-*DNAJB11* and ADPKD-*ALG5*.[95,96] In the context of this wide range of inherited disorders involving cystic kidneys, careful clinical evaluation and broad genetic testing can help ensure that the correct diagnosis is made.

Noninherited development of kidney cysts also can occur. Such development includes the appearance of a small number of simple cysts that can develop with aging,[64] or acquired cystic disease, a manifestation that often occurs in kidneys with severe CKD or after kidney failure, especially for those on long-term dialysis (Table 5).[97] In addition, certain medications, such as chronic lithium usage, can result in the development of multiple small kidney cysts.[98]

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

Obtaining a firm diagnosis in ADPKD is important for the appropriate management and treatment of the affected

Table 5 | Other disorders that present with kidney cysts

Gene	Disease	Inheritance	Overlapping with ADPKD	Distinguishing from ADPKD	Comments
Developmental disorders					
HNF1B	*HNF1B*-related kidney disease	AD	Cystic kidney disease	Congenital kidney and urinary tract anomalies, early-onset diabetes, pancreatic disease, elevated liver enzyme levels, and hypomagnesemia	Sometimes presents as ADPKD spectrum alone
JAG1, NOTCH2	Alagille syndrome	AD	Kidney cysts	Hepatic bile duct paucity; cholestasis; cardiac, skeletal, facial, and eye abnormalities; and dysplastic kidneys	A major feature can be infantile, small cystic kidneys and abnormal kidney function.
Collagen disorders					
COL4A1	Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC)	AD	Kidney cysts	Hematuria, retinal arterial tortuosities, muscular contractures, and brain small-vessel disease	Presentation with mild cystic disease and few other phenotypes has been described.[93,99,100]
COL4A3, COL4A4, COL4A5	COL4A-related diseases	AD and X-linked	Kidney cysts	Thinning of the glomerular basement membrane, microhematuria	Occasionally, kidney cysts are the major presentation.[93,94]
Urinary stone diseases (USD)					
CYP24A1, SLC34A3, HOGA1	A variety of USDs	AR (AD)	Kidney cysts	Predominant phenotype of kidney stones, nephrocalcinosis, and/or other mineralization	Usually limited cyst involvement[101–103]; may apply to other USDs
Autosomal dominant tubulointerstitial kidney disease (ADTKD)					
MUC1, REN, SEC61A1, UMOD	ADTKD	AD	Kidney cysts	Reduced kidney function, normal- to small-sized kidneys due to fibrotic kidneys; a few kidney cysts may be detected; no liver cysts	Hyperuricemia (low FE_{urate}) and gout are prominent in ADTKD-*UMOD* and anemia and gout in ADTKD-*REN*.
Recessive PKD					
PKHD1, DZIP1L, CYS1, PKD1	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 (CHF) rather than PLD	Later-onset kidney disease can mimic ADPKD, but kidneys usually do not increase in length over time and CHF is usually present. Biallelic *PKD1* changes can cause VEO to adult-onset disease.
PMM2	Hyperinsulinemic hypoglycemia and polycystic kidney disease (HIPKD)	AR	Kidney cysts	The kidney disease is ARPKD-like, but hyperinsulinemic hypoglycemia is also found; liver cysts are only rarely seen	Biallelic disease where at least one allele is the promoter variant (c.-167G>T); typical biallelic *PMM2* disease causes the congenital disorder of glycosylation type 1a (CDG1A)
Tumorous disorders					
FLCN	Birt-Hogg-Dubé syndrome	AD	Kidney cysts	Hair follicle hamartomas, kidney tumors, spontaneous pneumothorax, lung cysts	*FLCN* pathogenic variant described in person with "ADPKD" and lung cysts[88]
TSC1 TSC2	Tuberous sclerosis complex (TSC)	AD	Kidney cysts	Multisystem disorder with hamartomas in brain, skin, heart, kidneys (angiomyolipomas), and/or lung, plus CNS manifestations: epilepsy, learning difficulties, behavioral problems	Kidney cysts can be a major presentation with limited additional phenotypes.
PKD1/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 KF; mosaicism is common, which may be associated with less severe PKD[90,91]
VHL	Von-Hippel-Lindau syndrome	AD	Kidney and pancreatic cysts	Familial cancer syndrome with malignant and benign neoplasms in retina, cerebellum, spinal hemangioblastoma, RCC, pheochromocytoma, and pancreatic tumors	RCC develops from the kidney cysts.

Table 5 | (Continued)

Gene	Disease	Inheritance	Overlapping with ADPKD	Distinguishing from ADPKD	Comments
FH	Hereditary leiomyomatosis and renal cell cancer (HLRCC)	AD	Small kidney cysts	Papillary RCC, leiomyomata of the uterus, and cutaneous piloleiomyoma	Kidney cysts that can metastasize at a small size
Syndromic ciliopathies					
OFD1	Oral-facial-digital syndrome 1	X-linked	Kidney cysts in female patients	Malformations of the face, oral cavity, including cleft lip/palate, and digits, and PKD with abnormal kidney function; usually, lethal in male patients	The PKD can mimic ADPKD, and the facial and digital phenotypes can be minimal.
NPHP1 and other NPHP genes	Nephronophthisis (NPHP)	AR	Cortico-medullary cysts	Childhood presentation with echogenicity, loss of corticomedullary differentiation, small atrophic kidneys, and CKD	NPHP1, and other forms of NPHP, can first present in adulthood.
Many genes	Syndromic ciliopathies such as Joubert, Bardet Biedl, Meckel syndrome, and short rib thoracic dystrophy	AR	Kidney cysts	Often infantile or childhood disorders; a wide range of extrarenal 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 KF; kidneys are not enlarged	ACD is a risk factor for kidney cancer.

ACD, acquired cystic disease; AD, autosomal dominant; AR, autosomal recessive; CHF, congenital hepatic fibrosis; CKD, chronic kidney disease; CNS, central nervous system; KF, kidney failure; PKD, polycystic kidney disease; PLD, polycystic liver disease; RCC, renal cell carcinoma; TSC, tuberous sclerosis complex; USD, urinary stone diseases; VEO, very early onset.

person. Although we do not propose that genetic testing be conducted for everyone, genetic testing is an important part of the armament to be used to correctly diagnose ADPKD. Due to genomic duplication of the *PKD1* gene with 6 copies on the same chromosome containing a sequence of similar pseudogenes, the method of locus-specific long-range polymerase chain reaction and Sanger sequencing has been employed to screen this locus.[75,104] However, now gene capture and tNGS panels, specifically designed to screen PKD genes, have been shown to be a successful way to screen these genes.[105,106] These methods are cheaper and easier to use than the Sanger approach, and they can involve just the known ADPKD genes, a broader array of PKD and ciliopathy genes, or all known genes associated with kidney disorders (Table 6). Even broader approaches, such as WES, can be employed (although some concerns have been raised regarding *PKD1* coverage in WES panels[107]), with analysis initially focused on known ADPKD and/or PKD genes (PKD gene WES).[40] Whole-genome sequencing (WGS) is being used increasingly for clinical genetic screening, and it has the advantage of providing even coverage throughout the genome, with intronic and intergene regions also screened, but cost and data-analysis issues need to be considered (Table 6).[108,109] Currently, a PKD and/or nephrology tNGS panel is the most effective and the most cost-effective means to genetically screen people with suspected ADPKD, and we discourage use of very limited Sanger or NGS approaches, although further comparison of the broad-based approaches is required (see Research Recommendations). As well as base-pair changes, exon plus–sized deletions and duplications, and copy number variants should be tested in the analysis of the NGS and confirmed by multiplex ligation-dependent probe amplification (MLPA) or similar methods. Increasingly, health insurance companies or government entities paying for testing are covering the costs of the screening with no copayment or a limited copayment for the patient, although individual requests often are required.[110] This increased acceptance of genetic testing reflects its perceived value for obtaining a firm diagnosis and aiding in the management of the affected person.

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

Specific ACMG guidelines for reporting variants that are detected by means of NGS approaches have been adopted by clinical testing laboratories.[111] 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. The data are scored as being "strong," "moderate," or "supporting." The possible pathogenic categories are "pathogenic" or "likely pathogenic." Neutral categories are "benign" or "likely benign," whereas ones that do not score appropriately for a diagnostic or benign category are labeled "variants of uncertain significance (VUS)." This approach is employed to avoid

Table 6 | Genetic testing methods for screening for ADPKD and ADPLD

	Sequencing method			
Factors compared between methods	**Targeted next generation sequencing (tNGS) gene panel**	**Sanger sequencing**	**Whole exome sequencing (WES) slice[a]**	**Whole genome sequencing (WGS) slice[a]**
Descriptions	Exons and flanking intronic regions of candidate PKD genes captured and screened by NGS	Each PKD gene (exon) screened separately LR-PCR needed to screen the duplicated region of *PKD1*	Exons and flanking intronic regions of all genes captured and screened by NGS, priority analysis of known PKD genes	The whole genome is screened, priority analysis of known PKD genes
Genes screened	Panels can include coding regions of all known PKD and ciliopathy genes (n ~150) or all known kidney disease genes (n ~600)	Screening of major genes possible but impractical to screen more than a few genes	Initial analysis slice includes coding regions of all known PKD genes (n ~150)	Initial analysis slice includes genomic regions of all known PKD genes (n ~150)
Cost	Least-expensive method: Tiny fraction of the genome sequenced and so allows multiplexing for capture and NGS	Price per gene is expensive: The LR-PCR method is time-consuming and difficult	Moderately expensive: Only small fraction of the genome sequenced but less multiplexing options	Expensive: Whole genome sequenced
Flexibility	Data only obtained from sequenced genes	Data only obtained from sequenced genes	Genes not included in the slice can be retrospectively screened; helpful for periodic result reevaluation	Genes not included in the slice can be retrospectively screened; helpful for periodic result reevaluation
Bioinformatic workload	Moderate number of variants to evaluate	Low number of variants to evaluate	Moderate to high number of variants to evaluate	High number of variants to evaluate
Hard-to-screen regions	Coverage optimized for difficult regions, like the *PKD1* duplicated area, but some regions may still be difficult to screen. GC-rich regions (e.g., *PKD1* exon 1) and ones very similar to the pseudogenes may not be adequately screened	Good coverage of GC-rich and duplicated region of *PKD1* (with LR-PCR method) Allelic drop-out due to SNP under the PCR primer can result in variants not detected	Significant chance that regions with high homology with other regions (*PKD1* duplicated region) and GC-rich regions are not adequately screened (e.g., *PKD1* exon 1)	More even coverage of the genome, including GC-rich and duplicated regions
CNVs	CNV detection is possible	Generally, not detected. MLPA analysis required	CNV detection is possible	Most reliable analysis of CNV
Mosaicism	High read-depth: Mosaic screening possible	Not reliably detected	Moderate read-depth: Mosaic screening may be possible	Low read-depth: Mosaic screening not reliable
Noncoding regions	Not screened	Not screened	Not screened	Screened: Deep intronic pathogenic variants detected
Guidance	**Best method for primary screening**	**Method of choice for variant confirmation**	**Possible for primary screening, with flexibility of the genes screened**	**Follow-up for high probability cases not resolved by tNGS**

ADPKD, autosomal dominant polycystic kidney disease; ADPLD, autosomal dominant polycystic liver disease; CNV, copy number variant; GC, guanine–cytosine; LR, long-range; MLPA, multiplex ligation-dependent probe amplification; NGS, next generation sequencing; PCR, polymerase chain reaction; PKD, polycystic kidney disease; SNP, single nucleotide polymorphism.

[a]Slice analysis means initially analyzing genes associated with PKD and ciliopathies. Analysis of the complete WES or WGS as the initial screen is possible, but it is more expensive, highlights other variants that are unlikely to be relevant, including in reportable genes, and does not greatly increase the chance of obtaining a genetic diagnosis.

misdiagnoses based on limited data, because of the serious problems associated with misassignment of a monogenic disease diagnosis. The possible consequences of genetic testing and evaluation of variants are shown in Table 7. Periodic result re-evaluation is recommended as new evidence about specific variants and genes becomes available.

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

Clinical genetic testing in a person with ADPKD does not detect all pathogenic variants (probably ~75%[25]), and further study is needed to determine the yield in obtaining a genetic diagnosis from this testing. Although most pathogenic changes occur in the coding exons and flanking splicing regions, some changes occur 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 classified as being in the nondiagnostic VUS grouping.[111] ADPKD is highly allelically heterogeneous, with more than 2000 different pathogenic variants reported in the known genes,[112,113] with new, previously undescribed variants being identified often. For novel truncating changes, classification using the ACMG guidelines normally will place them in a pathogenic category.[111] However, for novel nontruncating changes, the type that represents ~35% of *PKD1* pathogenic variants,[5] the variant is often classified as a VUS. In some cases, showing coinheritance with the disease by segregating the variant in family members can allow reclassification of the variant into a diagnostic group. Functional studies also can be helpful, but few

Table 7 | Consequences of genetic testing by tNGS for people with typical or atypical ADPKD

Person tested	Results of the testing	Significance	Consequence	Follow-up	Comments
Typical ADPKD presentation (multiple bilateral cysts, kidney enlargement, CKD in older subjects, ± liver cysts); with or without a positive family history	P or LP variant is detected in a known ADPKD gene	A genetic diagnosis of ADPKD is made	Clinical decisions can be made based on the phenotypic and genetic results	Simple, Sanger testing of at-risk family members. If negative F/H, testing of parents may confirm a *de novo* mutation	This is the most likely outcome in this situation
	One or more VUS is detected in a known ADPKD gene(s)	A genetic diagnosis of ADPKD is not made	The clinical diagnosis should be sufficient to start treatment or enroll in a clinical trial, if warranted by disease severity	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	The existing ACMG guidelines often classify novel nontruncating variants as a VUS. As new information becomes available, reclassification to LP or LB may occur. Research studies may be helpful
	No significant variants are detected	A genetic diagnosis of ADPKD is not made	The clinical diagnosis should be sufficient to start treatment or enroll in a clinical trial, if warranted by disease severity	Consider rescreening of *PKD1* by Sanger analysis or WGS. If negative F/H, screen for mosaicism	P/LP variants, especially in *PKD1* may be missed by present screening methods. Research studies may be helpful
Atypical ADPKD presentation (multiple bilateral cysts, no kidney enlargement, no CKD, ± liver cysts); with or without a positive family history	P or LP variant is detected in a known ADPKD gene	A genetic diagnosis of ADPKD is made	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	Simple, Sanger testing of at-risk family members. If negative F/H, testing of parents may confirm a *de novo* mutation	Obtaining a firm genetic diagnosis occurs less frequently than in those with more typical disease
	One or more VUS is detected in a known ADPKD gene(s)	A genetic diagnosis of ADPKD is not made	PKD without kidney enlargement may limit treatment options and enrollment in clinical trials	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	The existing ACMG guidelines often classify novel nontruncating variants as a VUS. As new information becomes available, reclassification to LP or LB may occur. Research studies may be helpful
	No significant variants are detected	A genetic diagnosis of ADPKD is not made	The mild PKD may limit treatment options and enrollment in clinical trials	Consider rescreening of *PKD1* by Sanger analysis or WGS. If negative F/H, screen for mosaicism	P/LP variants, especially in *PKD1* may be missed by present screening methods. Research studies may be helpful
	A P/LP variant is found in another dominantly inherited PKD-related gene	A genetic diagnosis of the implicated disorder is made, if also consistent with re-phenotyping	The new diagnosis may change the management, surveillance, and treatment options of the person	Simple testing of at-risk family members by Sanger sequencing can be performed	This scenario is found at a relative low frequency

ACMG, American College of Medical Genetics and Genomics; ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; F/H, family history; LB, likely benign; LP, likely pathogenic; P, pathogenic; PKD, polycystic kidney disease; tNGS, targeted next-generation sequencing; VUS, variant of uncertain significance; WGS, whole-genome sequencing.

are presently available for the ADPKD genes. More variant reporting in databases, such as ClinVar or the ADPKD Variant Database, also can help reclassify VUS into diagnostic categories. More research is needed to improve the number of variants that can be diagnostically categorized, to create specific ACMG guidelines for the ADPKD genes.

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

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 (e.g., only VUS are defined), this should not be interpreted as indicating that the person does not have ADPKD. Therefore, management, treatment, and access to clinical trials should not be altered by these findings and should proceed as they would for any person clinically defined as having ADPKD.

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

For people with just a few cysts or an atypical imaging or extrarenal presentation, negative/VUS findings should not be interpreted as indicating a lack of a genetic cause of the kidney cysts, and management should proceed based on the clinical findings.

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, ~60 years) as a common outcome.[114,115] However, wide divergences from this typical outcome have been documented, from fetal demise to normal kidney function into old age.[38,116] Extrarenal manifestations, such as the occurrence of severe PLD or intracranial aneurysms (ICAs), are also highly variable. The severity of kidney disease likely is governed by factors specific for ADPKD and others associated with CKD progression, as illustrated in Figure 6. 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.

The fact that multiple factors influence kidney disease severity (Figure 6) should be discussed with the patient, in counseling. Both the gene involved (genic affect; Practice Point 1.4.1.1), and for ADPKD-*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 6; Practice Point 1.4.1.2). However, significant intrafamilial variability in kidney disease severity indicates that factors beyond the causative disease variant are important.[117,118]

In unusual situations, such as the *PKD1/TSC2* CGS[90,91] and ADPKD-*PKD1* and ADPKD-*PKD2* digenic disease,[72,74] documented in animal models and/or rare cases,[68,119,120] pathogenic germline variants in other genes have been shown to significantly influence the severity of the ADPKD-associated kidney disease. Recent data indicate that a CKD genome polygenic score (GPS) is of some prognostic value in ADPKD, suggesting that common genetic factors associated with CKD can modify the phenotype; however, the full extent to which both common and rare variants influence the severity of disease in typical ADPKD needs further study.[121] Likewise, biallelic disease has been demonstrated clearly as a cause of VEO-ADPKD,[38,67,69,70] but whether minor variants in the normal copy of the disease-causing gene influence the severity of kidney disease more generally is not clear. Good evidence also indicates that somatic variants to the normal allele of the disease-causing ADPKD gene occur, and possibly somatic changes elsewhere,[122–125] but whether variability of the timing and/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 likely important in ADPKD, including the sex of the affected person, the body habitus, and the level of salt intake (see also Chapter 3). Smoking generally is discouraged because of its multiple adverse effects on health, whereas normal exercise is encouraged (see Chapter 7).[126] Caffeine intake has been discouraged specifically in ADPKD, but the evidence supporting a detrimental effect on kidney disease progression is limited or is restricted to mainly animal models.[127–129] In animal models, kidney damage is a major factor influencing the rate of kidney disease progression[130,131]; however, the importance of acute kidney injury (AKI) to human disease progression has not been studied systematically. Likewise, data are limited on the role of comorbidities (e.g., diabetes, vascular-related changes,[132] or kidney stones) in 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 data are sparse about many of the minor genes involved. For the major genes *PKD1* and *PKD2, PKD1* consistently is associated with more severe kidney disease than is *PKD2*. The median age at the time of kidney failure was 54.3 years (95% confidence interval [CI]: 52.7–55.9 years) and 74.0 years (95% CI: 67.2–80.8 years), for ADPKD-*PKD1* and ADPKD-*PKD2*, respectively, in linkage-determined European families,[133] and 58.1 years (95% CI: 56.5–59.9 years) and 79.7 years (95% CI: 76.8–82.6 years)[35] or 58.0 years and 74.8 years in genetically resolved people in the Genkyst or Mayo Clinic cohort, respectively.[115] Other measures of severity of kidney disease, including estimated glomerular filtration rate

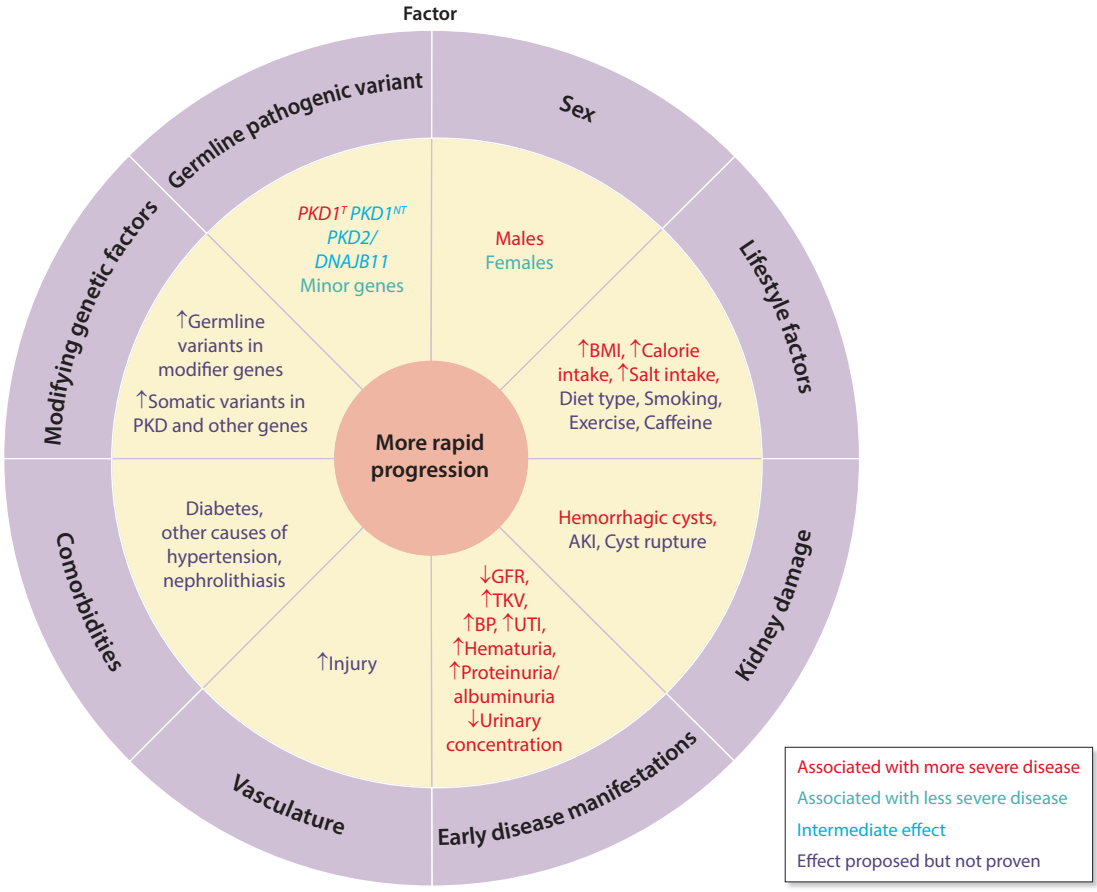


Figure 6 | Factors associated with the rate of disease progression in autosomal dominant polycystic kidney disease (ADPKD). AKI, acute kidney injury; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HTN, hypertension; NT, nontruncating pathogenic variants; PKD, polycystic kidney disease; T, truncating pathogenic variants; TKV, total kidney volume; UTI, urinary tract infection; ↑, increase in value associated with outcome; ↓, decrease in value associated with outcome. Early disease manifestations normally would occur before a patient reaches age 35 years.

(eGFR)/age and height-adjusted TKV (htTKV)/age are greater and smaller for ADPKD-*PKD2*, compared to ADPKD-*PKD1*, respectively.[5]

For the minor ADPKD genes, the greatest risk of kidney failure comes with ADPKD-*NEK8*, with people who are affected reaching kidney failure in childhood (at age 1–17 years), although a milder course of the disease is reported with certain alleles, and in the case of mosaicism.[22] An important point to mention is 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 to an ADPKD phenotype. In ADPKD-*DNAJB11*, a study of 77 affected people (23 pedigrees) found a median age at kidney failure of 75 years (range: 55–89 years).[19] More limited data are available for the other ADPKD genes, but those data indicate a moderate risk of kidney failure for ADPKD-*ALG9*[9] and ADPKD-*ALG5*,[11], and a low risk for ADPKD-*GANAB*[7] and ADPKD-*IFT140*.[10] The phenotypes of the genes with limited evidence of causing a monoallelic phenotype (Table 1) have yet to be fully determined. Also, data are limited regarding the penetrance of the kidney disease associated with the minor genes.[24,25] Therefore, knowing what gene is affected is of value when assessing the risk of kidney failure in ADPKD, but the true phenotypic range and penetrance are unknown for many minor genes.

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

At a population level, *PKD1* pathogenic variants that are predicted to truncate the encoded protein, compared with nontruncating variants, are associated with worse kidney outcomes. The Genkyst study found that the median age at kidney failure was 55.1 years (interquartile range: 48.5–62.1 years) for *PKD1* truncating variants, and 65.8 years (interquartile range: 53–76.5 years) for *PKD1* nontruncating variants.[36] However, the nontruncating group is heterogeneous, including likely fully inactivating variants and hypomorphic

variants generating some functional protein. Efforts to separate these groups by *in silico* studies, into those predicted to be more penetrant versus less penetrant, found that the median ages at kidney failure were 60.8 years and 66.2 years, respectively.[5,115] Multivariate analysis also including MIC, sex, baseline eGFR, and baseline body mass index (BMI) showed that 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 ADPKD-*PKD1* group, and 0.27 (95% CI: 0.150–0.497) for ADPKD-*PKD2* relative to truncating ADPKD-*PKD1*, but the more penetrant nontruncating ADPKD-*PKD1* group was not significantly different. In the largest study of *PKD2*, nontruncating variants were associated with a higher eGFR than were truncating variants.[134] Therefore, the type of pathogenic variant to the major genes is significant to future kidney outcomes; however, considerable variability exists at the level of the affected person. Employing genotype data with clinical indications, as in the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score, may help in making prognostic predictions.[36]

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

The severity of disease progression in affected family members, such as the age at kidney failure, provides some guidance to the likely outcome in other, including presymptomatic, affected family members.[135] This guidance is expected, as all affected family members usually 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.[117,118] Significant differences in disease presentation among affected family members, such as VEO-ADPKD, may indicate genetic complexity and represent an indication for conducting genetic testing.

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

Data on the importance of sex to the severity of ADPKD kidney disease are controversial, but generally, male sex seems to be associated with more severe disease. In the Mayo Clinic and Genkyst cohort studies, the age at kidney failure was 58.2 years and 63.9 years, and 62.8 years and 65.4 years, for males and females, respectively.[35,115] Corresponding male and female ages were 55.7 years and 59.4 years, respectively, for ADPKD-*PKD1*, and for ADPKD-*PKD2*, it was 71.2 years, and <50% of females experienced kidney failure.[115] In univariate analysis, male sex was associated with a greater risk of kidney failure (HR: 1.3; 95% CI: 1.0–1.4[36] versus HR: 1.59; 95% CI: 1.27–2.0).[115] In multivariate analysis that also considered age, mutational group, baseline eGFR, and BMI, the kidney failure HR for male patients, relative to that of female patients, was 1.41 (95% CI: 1.09–1.81).[115] We suggest that sex be considered when determining outcomes, and we advise using sex as part of the PROPKD score, but we understand that further study is required.

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

In animal models, low-calorie and specific diets, including a high level of water intake, have reduced the rate of kidney disease progression,[136–139] but the importance of these factors to the disease as it occurs in humans is still being investigated (Chapter 7). A related point is that obesity is a risk factor for the development and progression of CKD, but data are limited about its significance in ADPKD. In the HALT Progression of Polycystic Kidney Disease (HALT-PKD) Study A population, BMI categories (with excess 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 (SD) rates of TKV growth of 6.1% ± 4.7%, 7.9% ± 4.8%, and 9.4% ± 6.2%, respectively; $P \leq 0.001$.[140] In a multivariate model, the annual mean percentage (95% CI) increase of TKV growth for obese individuals, compared to those in the normal-weight category, was 2.70% (95% CI: 1.45%–3.95%), and the beta of annual eGFR decline was –0.08 (95% CI: –0.15 to –0.02). In a Mayo multivariate analysis, the HR for kidney failure during follow-up for a BMI 5 kg/m^2 greater was 1.119 (95% CI: 1.004–1.248): $P = 0.042$.[115] Overall, modest evidence indicates that body weight is associated with the rate of disease progression in ADPKD.

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

In the HALT-PKD Study A, using a linear mixed model, a significant association was observed of average urine sodium excretion (UNaE) and annual rate of TKV growth (0.43% per year for each 18-mEq increase in UNaE; $P < 0.001$).[141] Using a similar model in the HALT-PKD Study B, a greater annual rate of decline in eGFR was associated with salt-intake level (–0.086 ml/min per year for each 18 mEq/24 h increase in UNaE; $P < 0.001$). Also, an HR = 1.08, for each 18 mEq/24-h 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 study in The Netherlands, salt-intake level was significantly associated with an annual change in eGFR of –0.11 ml/min per 1.73 m^2 (95% CI: 0.20 to –0.02) per gram of salt.[142] Therefore, controlling the level of salt intake is likely of value in ADPKD (Chapter 7).

1.4.2 Ways to assess the severity of kidney disease progression

Different methods can be used to monitor the severity of kidney disease in ADPKD, and potentially, identify people with more rapid progression (Figure 7). ADPKD is a disease that

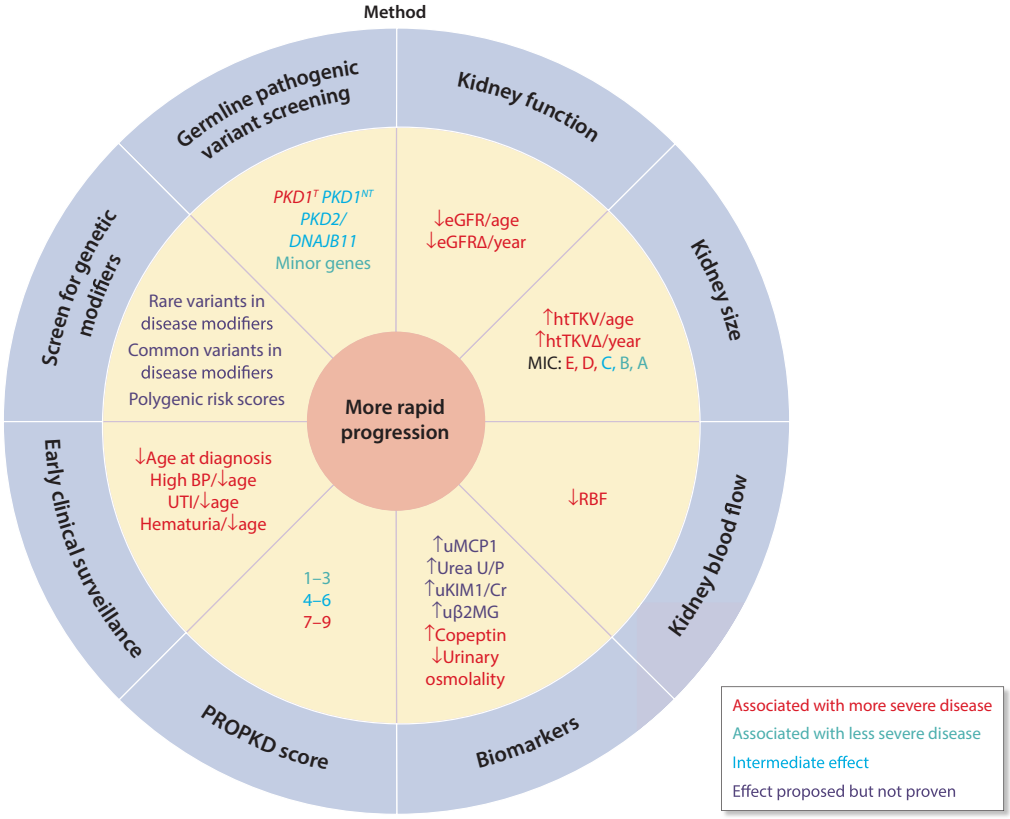


Figure 7 | Methods to assess the rate of kidney disease progression in autosomal dominant polycystic kidney disease (ADPKD). BP, blood pressure; eGFR, estimated glomerular filtration rate; hem; hematuria; htTKV, height-adjusted total kidney volume; MIC, Mayo Image Classification; NT, nontruncating; PKD, polycystic kidney disease; PROPKD, 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.

normally progresses over many decades, with kidney failure typically occurring later in life. Given that measurements of kidney function, such as eGFR determined from serum creatinine (SCr) level, are relatively insensitive to detect small reductions in function, other methods to monitor early-stage disease have been developed. The results of the CRISP study have shown that measuring the size of the kidneys, using MRI-determined htTKV, is the best biomarker in the early disease stages.[143] We therefore advise employing htTKV for prognostic purposes in early ADPKD. A simple way to employ htTKV is by using the MIC, which provides age-adjusted categories and helps to identify people with rapidly progressive disease (Recommendation 1.4.2.1).[32] Analysis of kidney function, however, also can 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 1.4.2.8). Early onset of ADPKD disease manifestations, such as hypertension and urological events, also can 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 1.4.2.6).[36] Other factors that may be helpful in identifying rapidly progressive disease are urine and serum biomarkers (Practice Point 1.4.2.9). Decreased renal blood flow (RBF) has been shown to be an early marker of severity of kidney disease, but this measure is difficult to use and calibrate, and we feel at this time that further research is required.[144,145] Identifying and utilizing genetic-modifying factors, including as a polygenic risk score, may also have predictive value.[121] Ultimately, a model that includes several of these factors is likely to have greater predictive power than the individual methods for assessing disease severity, but such a model is yet to be developed. One limitation is that most populations are enriched for White people, and further validation in more diverse populations is required.

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

Although TKV can be measured by ultrasound, CT, or MRI, MRI is most strongly advised for prognostics, owing to

its accuracy, reproducibility, and safety for TKV determination. MRI is noninvasive, does not use ionizing radiation, provides a high level of soft-tissue contrast, and does not need i.v. contrast (gadolinium-based contrast agents) for TKV calculation. These advantages are balanced by its cost and availability. CT is another option that is as accurate as MRI, but ionizing radiation is employed.[146]

TKV can be measured with the ellipsoid equation (π/6 x L x W x D), which requires sagittal and coronal length (L), width (W), and depth (D) data.[32] Although this method is 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.[32] Other ways to determine TKV using MRI include volume calculation by stereology,[147] planimetry tracings,[148,149] and semiautomatedly,[150] and fully automated approaches.[151] Methods that allow actual organ segmentation are more precise, with automated and semiautomated methods being 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 the favored approach, as it partially corrects for differences in kidney size that are due to height.[152]

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

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. Although kidney enlargement varies among people with ADPKD, data indicate that it occurs at a relatively consistent rate over time for a given affected person, as shown by the CRISP study.[143] In 214 participants, the mean (±SD) baseline TKV was 1060 (± 642) ml, and it increased by 204 (± 246 ml; 5.27% ± 3.92% per year; $P < 0.001$) over a 3-year follow-up period. A similar rate of increase of 5.5% per year (95% CI: 5.1%–6.0%) was found in the placebo group of the phase 3 Tolvaptan Efficacy and Safety in the Management of ADPKD and Its Outcomes (TEMPO 3:4) clinical trial.[28] 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 per year; $P <$ 0.001), whereas subjects with a baseline TKV of 750–1500 ml had a mean GFR decline of −0.69 (± 9.47) ml/min per year; $P = 0.57$).[143] In the latest follow-up of the CRISP population, the odds ratio (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.[153] 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 value (Supplementary Table S6[32,115,140,142,152–192]). Hence, kidney size, even from an early disease stage, has strong predictive value for determining later declines in kidney function and kidney failure. Given that the significance of htTKV is highly age-dependent, these data alone can be difficult to interpret; therefore, htTKV/age groups have been defined to categorize people with ADPKD according to the MIC.[32]

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

Ultrasound measurements of TKV in people with ADPKD, in the CRISP study, were found to be less accurate, compared to MRI measurements, as they lacked the precision necessary to measure short-term disease progression, such as that in clinical trials.[193] However, ultrasound did provide an estimate of TKV that reflected the severity of kidney disease in an individual person.[194] An analysis comparing kidney size (both htTKV and kidney length) measured by ultrasound versus MRI showed similar area-under-the-curve (AUC) values from receiver operator curves (ROCs) for predicting eGFR decline to CKD G3, for both measurements and both modalities.[156] However, the authors did not assess the difference in test accuracy between the 2 measures. Also, kidney-length data may be confusing if just a few large and/or exophytic cysts are present, as is true for MRI-determined "atypical" (class 2) cases. More recently, ultrasound ellipsoid measurements were found to underestimate TKV by 11%, and to misassign the MIC (more frequently to a lower class) in 22% of patients, compared with MRI manual segmentation.[195] Nevertheless, they predicted a high-risk MIC subclass (1C–1E), with a positive predictive value (PPV) of 98%, a specificity of 99%, a negative predictive value (NPV) of 95%, and a sensitivity of 94%. An average ultrasound kidney length >16.5 cm was highly predictive of being in MIC subclass 1C–1E only in people aged ≤45 years,[195] and this measure misclassified some people with rapid disease progression.[196] Therefore, ultrasound data may be used to estimate the severity of the ADPKD, but they are less precise and have been validated less than MRI or CT-based segmentation measurements, which are preferred when available and in cases of doubt.[196] One other option, if genotype is available but not MRI-determined htTKV, is to combine genotype and ultrasound-determined, height-adjusted mean kidney length.[197] See Chapter 9 also, regarding use of ultrasound for disease assessment in children.

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

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. Moderate evidence supports this recommendation.

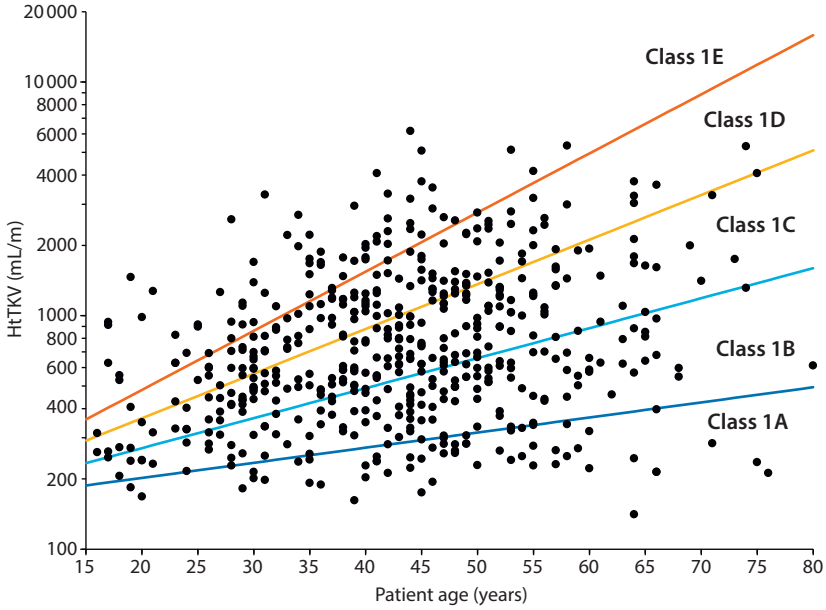


Figure 8 | The Mayo Imaging Classification divides height-adjusted total kidney volume (htTKV)/age into 5 different classes.[32] htTKV plotted against age is divided into 5 groups—classes 1A to 1E—reflecting kidney size and related to the severity of the kidney disease. Starting at a theoretical starting value of 150 ml/m at birth, annual htTKV growth rates are as follows: <1.5% for 1A; 1.5%–3.0% for 1B; 3.0%–4.5% for 1C; 4.5%–6.0% for 1D; and>6.0% for 1E. Reproduced from Irazabal *et al.*[32]

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%; 1E: >6%), starting from a theoretical equal htTKV at birth (Figure 8).[32] Hence, 5 htTKV groups are defined for classifying the size of the kidneys for people aged 15–80 years who have typical radiologic presentations. Important to note is that atypical radiologic presentations (MIC subclass 2), such as unilateral, segmental, asymmetric, or lopsided (MIC subclass 2A) or atrophic (MIC subclass 2B), are excluded from the predictive rubric, as the predictive nature of the MIC likely does not apply in these special situations (Figure 9). Likewise, the MIC should not be used for people affected by the minor genes. The MIC can be calculated using a web-based application: 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 on kidney volume estimated from stereology, together with patient height and age. The addition of present SCr level and demographic information also can allow estimation of approximate, future eGFR values.

Prognostic information in ADPKD is helpful for affected people and their nephrologists, ensuring that the care provided is based on the best estimates of the severity of the kidney disease. Such information also can be used to estimate whether kidney failure is likely, and if so, the approximate timing of this event. Use of this information ensures that approaches that can be taken prior to kidney failure, such as preemptive transplantation, are considered in a timely way. Strong evidence indicates that htTKV is the best existing prognostic biomarker in ADPKD, and that calculating the MIC is the easiest and simplest means to interpret and employ such data. The MIC also excludes people with atypical kidneys, for whom the relationship between htTKV/age and more rapid progression may not hold.[32] Abdominal imaging, MRI or CT, is needed to calculate the MIC. These imaging methods are noninvasive and are generally very safe, and gadolinium is not necessary in the MRI calculation of htTKV. However, contraindications that occur occasionally for MRI include presence of 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 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 S6[32,115,140,142,152–192]). The studies conducted mostly adequate multivariable analyses (based on analytic methods and a 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 a higher MIC, compared with a lower MIC. The grade of the certainty of evidence was downgraded from high to moderate, based primarily on some inconsistencies regarding how strongly each of the MIC classes was associated with change in kidney function.

From the initial study, the estimated frequency of kidney failure after 10 years of follow-up increased for each baseline MIC subclass (A to E)—by 2.4%, 11.0%, 37.8%, 47.1%, and 66.9%, respectively.[32] The study by Lavu *et al.* analyzed MIC

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

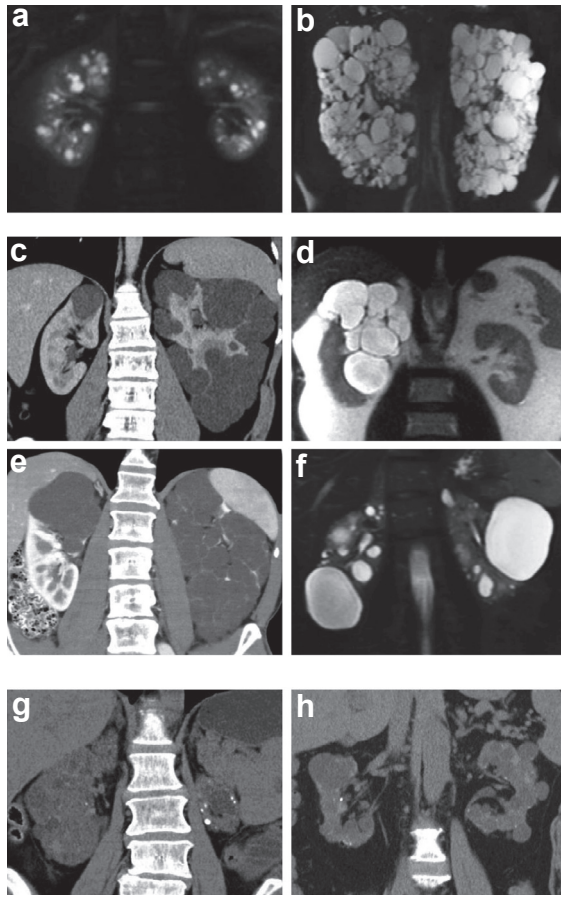


Figure 9 | The Mayo Imaging Classification (MIC) of autosomal dominant polycystic kidney disease (ADPKD; left panel) with examples (right panel) of (a,b) MIC subclass 1A and 1E, (c–f) MIC subclass 2A, and (g,h) MIC subclass 2B. Only the classification of typical ADPKD (class 1) has prognostic value. TKV, total kidney volume. Reproduced from Irazabal *et al.*[32]

as part of a multivariate analysis, and the risk of reaching kidney failure at any point during follow-up (average follow-up period of 16.8 years) was 97%, 92%, 78%, and 71% less for subjects in MIC subclass 1A, 1B, 1C, and 1D, respectively, compared to the risk in MIC subclass 1E subjects.[115] Consistent data were found in smaller studies with shorter follow-up periods.[153] This recommendation also is supported by data about the age at kidney failure for people in the different MIC subclasses. For instance, in an analysis of 1079 people with ADPKD-*PKD1* or ADPKD-*PKD2*, the Kaplan-Meier–determined age at kidney failure was, in years, 45.1, 55.6, 62.8, and 71.2, for MIC subclasses 1E to 1B, respectively, with <20% of people in MIC subclass 1A experiencing kidney failure.[115]

Analysis of eGFR trajectories in the CRISP study, and in a Mayo Clinic cohort, showed a range of rates of decline based on the MIC; usually, it was more rapid with a higher class (Figure 10). For the groups with a milder MIC subclass, the rate of decline also increased with age (consistent with a nonlinear decline), but for the most severe MIC subclasses, a more linear decline was seen (Figure 11).[115,198]

Values and preferences. Assignment of a MIC class requires CT or MR imaging, and determination of htTKV. Measurement of htTKV by automated or semiautomated methods, is strongly recommended, due to its accuracy, reproducibility, and speed. However, these methods require specific software that is presently lacking in availability at some locations, although this situation has continued to improve. The ellipsoid equation can be used to estimate htTKV from MR- or CT -determined kidney size measurements, but this method is less accurate than segmentation approaches.[199] Ultrasound, which is more widely available, can also be used to make htTKV calculations, but these generally are not as accurate as MR- or CT-determined values. The PROPKD score also can provide prognostic information if genetic data are available.

Considerations for implementation. The availability of methodologies should be considered in determining which to use in assessing outcomes in people with ADPKD. Although in settings with a high level of resources where MRI and CT generally are available, in low resource settings, ultrasound may be the only methodology available. Also, costs may influence decisions about which tests to employ

Predicted parameter	Age (yr)			
	20–30	30–40	40–50	50–60
Class A GFR Slope	109 (95–123) 0.77	110 (99–121) −0.63	97 (83–110) −2.03	69 (49–90) −3.42
Class B GFR Slope	113 (106–120) 0.21	108 (103–113) −1.19	89 (82–96) −2.58	56 (45–67) −3.98
Class C GFR Slope	113 (107–119) −0.52	101 (96–106) −1.92	75 (68–82) −3.32	35 (24–45) −4.71
Class D GFR Slope	119 (112–125) −1.97	92 (87–98) −3.37	51 (44–59) −4.77	−3.23 (−15.73–9.26) −6.16
Class E GFR Slope	103 (97–110) −3.25	64 (57–71) −4.65	10 (0–21) −6.05	0

Figure 10 | Predicted glomerular filtration rate (GFR) values, slopes, and paired differences between predicted and observed GFR at different ages, using a polynomial model. Units of GFR are ml/min per 1.73 m^2 (95% confidence interval); slopes are ml/min per 1.73 m^2 per year. Positive values mean GFR increase. Adapted from Yu *et al.* 2020.[153]

Predicted parameter Mayo Imaging Class	Age (yr)			
	25	35	45	55
MIC-1A eGFR Slope	100 (90–108) 0.13	98 (92–104) −0.47	91 (85–95) −1.07	77 (72–81) −1.67
MIC-1B eGFR Slope	94 (89–99) −0.13	89 (86–93) −0.81	78 (75–82) −1.48	59 (56–65) −2.16
MIC-1C eGFR Slope	106 (102–111) −1.90	86 (82–89) −2.21	62 (59–65) −2.53	35 (32–38) −2.84
MIC-1D eGFR Slope	105 (100–110) −2.73	77 (74–81) −3.03	45 (42–49) −3.32	<15 −3.62
MIC-1E eGFR Slope	86 (81–92) −3.92	50 (45–55) −3.38	19 (<15–24) −2.84	<15 −2.30

Figure 11 | Predicted estimated glomerular filtration rate (eGFR) values and slopes by Mayo Imaging Classification (MIC) at different ages, using a polynomial model. Units of GFR are ml/min per 1.73 m^2 (95% confidence interval); slopes are ml/min per 1.73 m^2 per year. Positive values mean GFR increase. Adapted from Lavu *et al.* 2020.[115]

and in what order. Thus, use of appropriate and available technology is important in obtaining images upon which to base prognostic information in people with ADPKD. Imaging may be repeated annually, or at 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.[32] Repeating the measurement of htTKV after 1 year can provide assurance that the initial image classification was correct. In most cases that lack other indications, imaging studies can be obtained less frequently (e.g., every 3–5 years).

Rationale

Calculating the htTKV from MRI 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 whether the person has a typical or an atypical imaging pattern, and for those with a typical pattern, their MIC subclass (1A–1E). Moderately strong evidence indicates that the MIC is correlated with future decline in kidney function, and the timing of kidney failure. The MIC calculator, with the addition of SCr and basic demographic data, also allows estimation of future

eGFR values. This categorization can be used to select subjects for clinical trials, and it may help to determine the best treatment options for people with ADPKD, including use of tolvaptan (Chapter 4).

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

Atypical (or class 2) ADPKD includes affected people who present as follows: with unilateral, segmental, asymmetric, lopside (MIC subclass 2A), or bilateral atypical presentation (MIC subclass 2B) (Figure 9[32]). MIC-based prognostics are not applicable in people with these atypical imaging patterns, because atrophy (MIC subclass 2B) can be associated with abnormal kidney function without enlargement, and kidney enlargement due to just a few large cysts (MIC subclass 2A) usually leaves a sufficient volume of functioning parenchyma for kidney function to be normal.

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

The MIC was developed mainly in a population of people with causal mutations in *PKD1* and *PKD2*, or who are genetically uncharacterized but have typical disease, and therefore, it is not designed to assess people who have ADPKD that is due to pathogenic changes in the minor genes. Often people from this group are classified as atypical, because just a few large cysts account for the kidney enlargement (MIC subclass 2A; e.g., ADPKD-*IFT140*[10]) or significant fibrotic atrophy, decreased kidney size, and sometimes abnormal kidney function (MIC subclass 2B) is seen (e.g., ADPKD-*DNAJB11*[8,19] or ADPKD-*ALG5*[11]). However, even if people with minor gene pathogenic variants are classified as typical (MIC subclasses 1A–1E), the MIC-based predictions should not be considered reliable in these cases. If no genetic information is available and the kidneys are classified as typical (MIC subclasses 1A–1E), the MIC predictions can be applied.

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

As highlighted above, the gene causing ADPKD and the variant type for *PKD1* is associated with the severity of kidney disease. Similarly, the affected person's sex also has an association with kidney disease outcomes, with male patients, on average, experiencing earlier kidney failure. The onset of hypertension in people with ADPKD occurs, on average, at ages in the early 30s, and being hypertensive before age 35 years has been defined as a risk factor for more rapid disease progression. Occurrence of hematuria or urinary tract infections (UTIs) also have been associated with a lower level of kidney function.[114] The PROPKD study[36] developed an algorithm based on these factors, which are associated with poorer outcomes (Figure 12), and its prognostic value has been replicated in an independent cohort (Figure 13).[200] This simple scheme can be useful in identifying people at risk for rapidly progressive disease, and it can be employed when kidney imaging data are not available. However, a point to note is that genotype data are required, and categories cannot be assigned reliably for people aged <35 years if they are not already hypertensive or have not had a urological event. When the information is available, considering both the MIC and the PROPKD score can be helpful in stratifying disease severity in people affected by ADPKD. Disease outcomes in people in MIC subclass 1C are heterogeneous, and applying

Variable	Points for PROPKD score
Sex	
Female	0
Male	1
Hypertension before age 35 yr	
No	0
Yes	2
≥1 urologic event before age 35 yr	
No	0
Yes	2
Pathogenic variant	
PKD2	0
PKD1 nontruncating	2
PKD1 truncating	4

Figure 12 | The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) algorithm. Low risk: 0–3; intermediate risk: 3–6; high risk: 7–9. A PROPKD score of ≤3 points allows for instances of kidney-failure onset before age 60 years to be eliminated, with a negative predictive value of 81.4%. Conversely, a PROPKD score of >6 points forecasts kidney-failure onset before age 60 years, with a positive predictive value of 90.9%. Urological events include gross hematuria or cyst hemorrhages, cyst infections, and flank pain related to cysts.

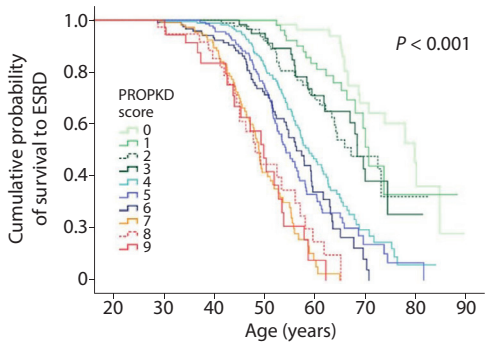


Figure 13 | The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score enables stratification of risk of progression to kidney failure in people with autosomal dominant polycystic kidney disease. Kidney survival is based on PROPKD, with scores ranging from 0 to 9 points. ESRD, end-stage renal disease. Reproduced from Cornec-LeGall *et al.* 2016.[36]

the PROPKD score has been shown to have added value.[200] Conversely, the PROPKD intermediate-risk group is also heterogeneous, and MIC can provide helpful stratification.

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

Although 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 recent studies have shown the value in these data. Kline *et al.*[201] showed that the addition of texture analysis (specifically entropy, correlation, and energy) to a prediction model improved the prediction of CKD G3a and G3b, and a 30% decline after 8 years of follow-up. Bae *et al.*[155] analyzed htTKV after excluding the volume of exophytic cysts for people with either MIC subclass 1 or 2 and showed improved predictive performance, compared with standard htTKV, regarding development of CKD G3 during follow-up. This method may allow some people with MIC subclass 2A to be assessed by the adjusted MIC as being in category MIC subclass 1. Riyahi *et al.*[187] found that the number of hemorrhagic cysts detected in MRI improved the 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.[202] In a study of CRISP study participants, total cyst number and cyst parenchyma surface area showed superior prediction, compared to TKV, of the slope of eGFR decline, kidney failure, and CKD G3a, G3b, and G4.

When it is available and has been validated, this additional imaging information has the potential to be valuable, providing additional ADPKD prognostic markers. Further development employing artificial intelligence is likely to improve the predictive power of image analysis.

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

Decline in kidney function is an age-related phenomenon in ADPKD. Classically, this has been proposed to be characterized by preserved function for several decades before a steep decline in the decade or so before the onset of kidney failure.[203] However, more recent data of plotted trajectories have shown that the rate of decline and associated values at particular ages (age groups) can differ among patient groups.[115,198] For instance, a more linear decline from an earlier age is suggested for the more severe MIC subclasses (1C–1E) and truncating *PKD1* pathogenic variants, whereas the groups with milder disease have the more traditional, "reverse hockey stick" trajectory. In the systematic analysis for this guideline, 11 of 17 studies were found to show an association between eGFR and future outcomes (Supplementary Table S6[32,115,140,142,152–192]). For instance, in multivariate analysis of 608 people with ADPKD-*PKD1* or ADPKD-*PKD2*, an eGFR that was 10 ml/min per 1.73 m^2 lower at baseline resulted in a 55% higher risk of kidney failure at any point during follow-up (average follow-up length: 16.8 years).[115] Various guidelines have included measurements of kidney function related to age as part of the criteria to identify people with rapidly progressive disease. In the European Renal Association (ERA) Workgroup for Inherited Kidney Diseases (WGIKD) and The European Rare Kidney Disease Reference Network (ERKNeT) position statement, eGFRs compatible with rapid progression were as follows: any, ages 18–39 years; <90 ml/min per 1.73 m^2, ages 40–44 years; <75 ml/min per 1.73 m^2, ages 45–49 years; and <60 ml/min per 1.73 m^2, ages 50–55 years.[204] Cutoffs for below-average eGFRs, or evidence for early decline, in the data of Lavu *et al.*, were approximately as follows: <90 ml/min per 1.73 m^2, age 25 years; <80 ml/min per 1.73 m^2, age 35 years; <60 ml/min per 1.73 m^2, age 45 years; and <30 ml/min per 1.73 m^2, age 55 years.[115] However, as many people who will reach kidney failure by age 65 years 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 guidelines have suggested that it can be helpful in identifying people with rapidly progressive disease.[204] A relatively consistent average decline in eGFR has been described in various cohorts, including the following: the HALT-PKD Study A group (aged 15–49 years at baseline), –3.5 ml/min per 1.73 m^2 per year in the standard BP group; approximately –3.9 ml/min per 1.73 m^2 per year in the HALT-PKD Study B group (aged 18–64 years); –3.7 ml/min per 1.73 m^2 per year in the TEMPO 3:4 control group (aged 18–50 years); and –3.61 ml/min per 1.73 m^2 per year in the Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) study (subjects aged 18–65 years).[28,29,205,206] 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 year.[203] Many of these studies selected for people with more rapidly progressive disease, and in the less selected population in the Irazabal *et al.* 2015 study,[32] the moderate group, with MIC subclass 1C, had an average decline of –2.63 ml/min per 1.73 m^2 per year, with declines of –2.63 and –2.43 ml/min per 1.73 m^2 per year for male and female subjects, respectively. However, the level of decline can change over time and is related to the MIC.[115,198] The ERA WGIKD/ERKNeT position statement concluded that an eGFR rate of decline of –3 ml/min per 1.73 m^2 per year indicates rapidly progressive disease.[204] This conclusion 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 ≥4 years.

The Work Group considers that measurement of the rate of decline of eGFR is useful in determining kidney disease severity in people with ADPKD, but multiple measurements over a significant period are needed. However, similar information can be obtained from comparison of age-adjusted

eGFR data for the affected person to reference data.[115,198] 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.[115] When a discrepancy is present between TKV and eGFR data, with a lower eGFR than expected, further analysis, including genetic testing, may be helpful.

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, considerable efforts have been made to develop better prognostic and treatment-monitoring urine and serum biomarkers in people with ADPKD.[157,166,167,207–213] However, at this stage, most such biomarkers have not outperformed the traditional means of monitoring kidney function—SCr, and cystatin C levels—and the development of improved biomarkers is an area for future research.

Research recommendations

- Compare Sanger, tNGS, WES, and WGS on control ADPKD populations to highlight the strengths and weaknesses of each approach.
- Determine more clearly the yield from genetic testing.
- Improve the ACMG guidelines for the ADPKD genes, to reduce the number of variants placed in the nondiagnostic category of VUS.
- Determine all the genes associated with the ADPKD and ADPLD phenotypes. Also, establish the full phenotype and penetrance of the minor genes required to cause cysts and reduction in eGFR.
- Determine more clearly the extent to which the type of *PKD1* pathogenic variant influences the resulting kidney phenotype.
- Determine how artificial intelligence may be helpful in processing large amounts of genetic data to help classify genetic variants based on training from large datasets.
- More carefully assess and validate ultrasound-based measurements as prognostic markers in ADPKD.
- Examine techniques that employ artificial intelligence to fully mine the information in radiologic images.
- The importance of sex as a risk factor for disease severity needs further study.
- Identify rare germline genetic variants, beyond the disease-causing gene, that influence the severity of ADPKD.
- Identify rare germline genetic variants in the normal copy of the disease-causing gene that influence the severity of ADPKD.
- Identify common genomic variants that influence the severity of ADPKD and determine the prognostic value of polygenic risk scores.
- Determine if somatic variants to the disease-causing gene and other genetic factors influence the severity of kidney disease.
- Determine the extent to which caloric restriction and/or specific diets influence the severity of kidney disease in ADPKD.
- Establish whether smoking influences the severity of kidney disease in ADPKD.
- Determine whether regular exercise influences the severity of kidney disease in ADPKD.
- Determine whether caffeine consumption influences the severity of kidney disease in ADPKD.
- Determine whether AKI is a factor that significantly worsens the kidney disease in ADPKD.
- Determine whether comorbidities, such as diabetes and kidney stones, influence the rate of kidney disease progression.
- Determine whether vascular disease is an important factor influencing kidney disease progression.
- Determine whether RBF can be measured more simply and is useful as an early prognostic marker.
- Identify and validate better urine and serum biomarkers of ADPKD progression.
- Identify and validate better predictive urine and serum biomarkers of ADPKD treatment.
- Develop a model that includes multiple imaging, and genetic, clinical, and biomarker inputs to better predict disease outcomes in ADPKD.
- Develop new prognostic scores and validate them in specific populations.

Chapter 2: Kidney manifestations

2.1 High blood pressure

High blood pressure (BP) is the most common and earliest clinical manifestation of ADPKD.[214] The majority of people with ADPKD are diagnosed with high BP before age 30 years, 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, and kidney stones.[143] Given that death in people with ADPKD most commonly is due to cardiovascular causes, continual surveillance of BP levels in people with ADPKD may 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 14).

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 they are complementary to pharmacotherapy in those with 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.[215]

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

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

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

The above BP measurement and monitoring methods have been recommended for the CKD population but should be equally valid for people with ADPKD.

Practice Point 2.1.3: Healthy dietary and lifestyle interventions should be incorporated into 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 intakes, 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-PKD trials (studies A and B), a lower level of dietary sodium intake, measured by 24-hour urinary sodium excretion, was associated with more favorable kidney disease outcomes.[141,205] Specifically, a linear mixed model showed a significant association with the annualized rate of TKV growth in the HALT-PKD Study A population (0.43% per year for each 18 mmol of daily urinary sodium excretion; $P < 0.001$), and a Cox proportional hazards model showed a significant association of the averaged level of 24-hour urinary sodium excretion with an increased risk of reaching the composite endpoint (eGFR, kidney failure, or death).[141]

This practice point is consistent with the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease*[215] and the *KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease*.[216] Dietary sodium restriction in both the CKD population and the 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 combination with antihypertensive agents, including renin-angiotensin system inhibitors (RASi). However, sodium intake may need to be adjusted in some situations (e.g., in hot climates; in occupational settings with low levels of fluid intake; for runners).

Other lifestyle interventions, including adoption of a heart-healthy diet, moderate regular physical activity, weight loss among those who are overweight or obese, and reduction of alcohol consumption have been demonstrated in randomized controlled trials (RCTs) to lower BP in the general population.[215] Smoking cessation may improve endothelial dysfunction and help to normalize BP in people with ADPKD.[217] Regular exercise, stress reduction, and maintenance of ideal body weight may help to keep BP in the normal range, as they can in 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 BP levels.[157]

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 of ≤110/75 mm Hg as measured by HBPM, if tolerated (*1D*).

Hypertension in ADPKD		
Monitoring	**Non-pharmacologic interventions**	**Medical management**
• Standardized office BP measurement in preference to routine office BP measurement • HBPM is preferred to office only measurements • Consider ABPM in children and adults with difficult BP control, LVH, proteinuria, or declining kidney function but normal office BP readings • Consider work up for secondary high BP when >3 BP medications are needed in the setting of medication and dietary compliance	• Reduce dietary sodium including minimizing processed foods • Optimize body weight with a healthy diet and regular exercise • Optimize pain management	• Inhibition of RAS provides the cornerstone of BP management and includes the use of an ACEi or ARB • Optimize BP with a 2nd-line agent, if needed • Individualized therapy is indicated

Figure 14 | Blood pressure (BP) management in autosomal dominant polycystic kidney disease (ADPKD). ABPM, ambulatory BP-monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HBPM, home BP-monitoring; LVH, left ventricular hypertrophy; RAS, renin–angiotensin system.

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

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 on the safety and tolerability of targeting the lowering of 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.[205] 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 treatment alone, as well as standard (120/70 mm Hg to 130/80 mm Hg) versus low (95/60 mm Hg to 110/75 mm Hg) BP targets on TKV. Other secondary outcomes also were included in this trial (i.e., slope of eGFR decline, LVMI, and albuminuria). BP targets were assessed using HBPM in this trial.

The study found no difference in the treatment effects of 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 per year; $P < 0.0010$), and a reduced urinary albumin excretion rate (–3.77% per year vs. 2.43% per year; $P < 0.001$), but with no significant difference in the slope of eGFR decline (–2.7 vs. –3.1 ml/min per 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 those in the standard BP group.

A point that should be noted is that more people with *PKD2* mutations were in the low-BP versus in the standard-BP group (19.8% vs. 13.1%), which potentially could skew the results in favor of the low-BP group, as people with *PKD2* mutations tend to have milder disease. When high-risk individuals (i.e., those with MIC subclass 1D or 1E) were evaluated in HALT-PKD Study A, the impact of randomization to a low-BP group (<110/75 mm Hg) was even greater, with a significant impact on the slope of eGFR decline, as well as an increase in TKV.[391]

Several other clinical trials also examined the effects of standard versus rigorous BP control on kidney and cardiac outcomes in people with ADPKD who are aged <50 years, with mixed results,[203,218,219] but they were limited by their small sample size ($n < 100$ per arm),[203,218,219] a *post hoc* subgroup analysis,[203] and inadequate control of confounding factors.[203,218,219] 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, whereas 2 studies showed a slower rate of increase in LVMI associated with vigorous BP control.[218,219]

Certainty of evidence. The overall certainty of evidence was graded as very low, due primarily to the sparseness of evidence for the most critical and important outcomes of interest (Supplementary Table S7[203,205,218,219]). The grade of the certainty of evidence for most outcomes also was 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). The grade of the certainty of evidence was low for the critical outcome of CKD progression, despite the sparseness of data for any given measure, due to inconsistency in measures across studies. The grade of the certainty of evidence was low for other critical outcomes, due to sparseness of data or a high level of imprecision. The grade of the certainty of evidence was low for the important outcome of change in LVMI in adults, because the evidence is derived mainly from one trial, the HALT-PKD Study A (although this trial was relatively large and was methodologically sound), whereas other small studies provided very low levels of evidence.

Given that the grade of certainty of evidence is low, and is for only a single critical outcome and a single important outcome (in adults), we concluded that overall, the grade of the certainty of evidence is very low.

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 the patient burden of HBPM. Although some people will find HBPM to be challenging and unacceptable, the benefits of this recommendation likely outweigh its potential inconvenience, and we believe that many well informed people with ADPKD would be interested in benefitting from intensive BP control and HBPM.

Resource use and costs. This recommendation will require extra resources, including access to HBPM and a time commitment by both people with ADPKD and their healthcare providers, 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 people aged 18–49 years with CKD G1–G2 and high BP (>130/85 mm Hg) who wish to pursue an intensive BP-control strategy to treat ADPKD. Any person interested in this treatment option should be informed about its potential risks and benefits, as well as the advantages of HBPM, with its associated costs, training, and time commitment. Regular BP measurements in both the prone and then the standing position, to assess postural hypotension, may minimize the risks of excessive BP control. Regular monitoring is defined as weekly measurement during the initial implementation, and then monthly measurement after stable BP control has been achieved.

For people with ADPKD aged 18–49 years with CKD G1–G2 whose BP falls between 110/75 mm Hg and 130/85 mm Hg, an individualized approach to BP control using shared decision-making between individual patients and their healthcare providers is appropriate.

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, and a greater decline in LVMI and urinary albumin excretion.[205] Furthermore, the intensive BP control was safe and tolerable, similar to that in the control group treated to a moderate level of BP control (130/85 mm Hg). Although currently no evidence supports the use of intensive BP control in slowing CKD progression in ADPKD, strong evidence indicates that intensive BP control in people with CKD is generally safe and is likely to be beneficial in terms of 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 aged ≥50 years with any stage of CKD (CKD G1-G5), we suggest a target mean systolic blood pressure (SBP) of <120 mm Hg, if tolerated, as assessed using standardized office BP measurement (*2C*).

This recommendation places a higher value on one large RCT that showed that targeting a mean SBP to <120 mm Hg (vs. <140 mm Hg) in people with CKD without diabetes was associated with a reduced incidence of cardiovascular events and all-cause mortality. This recommendation places a lower value on the increased risk of mild adverse events in the same trial. The recommendation is Level 2, because of a lack of evidence with a high grade of certainty used to evaluate the optimal BP target in late stages of ADPKD.

Key information

Balance of benefits and harms. Trial evidence that can be used to evaluate the optimal BP target in late stages of ADPKD is lacking. One large RCT conducted in people with CKD without diabetes, and excluding people with ADPKD, the Systolic Blood Pressure Intervention Trial (SPRINT), showed that targeting a mean SBP to <120 mm Hg (vs. <140 mm Hg), as assessed by standardized office BP measurement, is associated with reduction of the incidence of cardiovascular events and all-cause mortality, but with no difference in kidney outcome.[220] However, targeting a mean SBP <120 mm Hg was associated with an increased risk of the incidence of adverse events, including hypotension, syncope, electrolyte abnormalities, and AKI, but not injurious falls. A trial that was conducted in people with ADPKD (but mean [SD] age 49 (8) years and mean [SD] eGFR 48 (12) ml/min per 1.73 m^2), the HALT-PKD B trial, had a BP target of 110–130/70–80 mm Hg, which was very well tolerated.[206] This recommendation reflects a balance of the potential benefits of achieving the target BP goal and its associated risk of the occurrence of adverse events.

Certainty of evidence. The certainty of 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, whereas the level of effect on kidney failure is low, as described in the *KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease*.[215] A point to note is that the mean (SD) age of the participants of the SPRINT trial was 67.9 (9.4) years, which is older than the age of most people with ADPKD and CKD G3–G5. The certainty of evidence for people with CKD without diabetes from the KDIGO 2021 BP Guideline was judged to be moderate. After considering the evidence used in the KDIGO 2021 BP Guideline, together with the evidence from trials in people with ADPKD who were mostly aged <50 years and had less advanced CKD, the certainty grade was downgraded to low, due to the indirectness related to studying different populations.

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

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

A high grade of certainty of evidence to evaluate the optimal BP target in late stages of ADPKD is lacking. The SPRINT trial, the only RCT that examined the optimal BP target in people with CKD without diabetes (but that excluded people with ADPKD), found that targeting a mean SBP of <120 mm Hg (vs. <140 mm Hg), as assessed by standardized office BP measurement, is associated with a reduction in the incidence of cardiovascular events and all-cause mortality, but with no difference in kidney outcome.[220] A further point to note is that the trial participants were older than most people with ADPKD and CKD G3–G5, and that targeting a mean SBP of <120 mm Hg was associated with an increased risk of the occurrence of adverse events, including hypotension, syncope, electrolyte abnormalities, and AKI, but not injurious falls. Our recommendation reflects a balance of benefits and harms, as well as uncertainty of evidence, and it is consistent with that from the *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease*,[215] but has a low level of certainty of evidence, due to the indirectness related to questions about the applicability of this evidence to people with ADPKD.

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*).

This recommendation places a relatively high value on the kidney and cardioprotective effects of RASi in people with CKD. The grade of certainty of evidence for this recommendation is low because of limited evidence from RCTs 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 generally are underrepresented in these trials.[215] Although activation of systemic and local renin-angiotensin system (RAS) in ADPKD has been proposed to promote cyst growth and CKD progression,[221] definitive RCTs to confirm a class-specific kidney-protective effect of RASi in people with ADPKD have not been performed. A few comparative studies of RASi versus other antihypertensive agents were limited by their small sample sizes and mixed results.[222–226] The only large trial of antihypertensive therapy performed in people with ADPKD, the HALT-PKD A and B studies,[205,206] 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 people with ADPKD places a relatively high value on the cardioprotective benefits of RASi in CKD and on the demonstrated safety and tolerability of these agents.[205,206,215]

Certainty of evidence. The overall certainty of evidence regarding the comparison of RASi versus other antihypertensives was graded as low, due primarily to sparseness of evidence for any given drug comparison and a lack of evidence for most critical and important outcomes of interest (Supplementary Table S8[222,224,226]). The studies had some methodological concerns, related mostly 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 effects similar to one another, and that non-RASi (beta-blockers and calcium-channel blockers) had effects similar to one another, we found a moderate grade of 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 grade for certainty of evidence. No studies addressed other critical outcomes. Based on a single, small study, the grade of the certainty of evidence was very low for the important outcome of LVMI. No studies addressed other important outcomes. With a moderate grade of certainty of evidence for only one critical outcome (BP), and a low grade of certainty of evidence for another critical outcome, CKD progression, and a grade of no or very low

certainty of evidence for other outcomes, we concluded that overall, the grade of certainty of evidence is low.

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 data with the best certainty grade 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 a 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 levels should be checked within 2–4 weeks of the initiation or dose increase of RASi. Hyperkalemia associated with the use of RASi often can 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 the SCr level rises by >30% within 4 weeks following initiation or a dose increase. However, dose reduction or discontinuation of an 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 they reach age 30 years, when kidney function is usually still normal or near normal (eGFR >80 ml/min per 1.73 m^2). A significant correlation exists 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, a cause similar to that of high BP in people with bilateral renal artery stenosis. Thus, the biological rationale for the use of RASi in people with ADPKD is strong. However, whether RASi confers a class-specific effect in improving kidney outcomes in ADPKD, beyond that of BP control, is unclear. Directly comparative studies between RASi versus other classes of antihypertensive agents are few and have shown mixed results; most were limited by multiple methodological concerns, including small sample size and lack of control for biases and confounding.[222,227] Nevertheless, RASi was found to be safe and well tolerated in the HALT-PKD A and B studies, and it conferred a cardioprotective effect in RCTs with people with CKD, making it a reasonable first-line agent for high-BP treatment in people with ADPKD.

We agree with the following statement from the *KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD* and feel that this recommendation should apply to people with ADPKD.[215]

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*).

A growing body of evidence indicates that in people with CKD, with or without diabetes, RAS blockade using a combination of ACEi, ARB, and DRI does not lead to long-term kidney or cardiovascular benefits, despite leading to a reduction of proteinuria in the short term. RAS blockade 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 with people with CKD.[215] However, a point that should be noted is 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 combined ACEi and ARB treatment, versus ACEi treatment alone, in both early and late stages of ADPKD.[205,206] Thus, dual-RAS therapy should not be used in people with ADPKD.

Practice Point 2.1.5: 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 a person demonstrates having BP that is difficult to control with ≥3 drugs that are optimally dosed, consideration of evaluation for secondary causes of hypertension other than ADPKD is reasonable. Medication compliance and dietary sodium discretion should be confirmed. In addition, people with symptoms or clinical findings consistent with secondary causes of hypertension also should be evaluated for secondary causes of hypertension.

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

Proteinuria is uncommon in people with ADPKD, occurring in <20% of adults, and typically being low grade (<0.5 g/d). 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 proteinuria (i.e., >2–3 g/d), particularly in people with controlled hypertension, should signal the likelihood of a

second coexisting kidney disease, such as glomerulonephritis or diabetic nephropathy.

Research recommendations

- Studies are needed to determine whether the BP target of 110/75 mm Hg is beneficial in older adults who have ADPKD, high BP, and reduced kidney function, as it was for those who participated in the HALT-PKD Study B, in which 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 people with ADPKD.
- Studies are needed to determine whether other classes of antihypertensive agents or other cardiorenal protective medications, such as 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 is thought to be related to the kidneys and lasts longer than 3 months.[228,229] Such pain can be caused by renal capsule distention or traction on the renal pedicle, secondary to cyst expansion,[229,230] or can occur following an episode of acute pain (such as that originated by cyst infection or cyst hemorrhage) that results in nociceptive stimulation.[231] Such pain can be aggravated by mechanical back pain due to abnormal posture from cystic kidney enlargement.[230–232]

The severity of chronic pain shows little correlation with kidney volume, so people with mild or moderate cysts may occasionally develop disabling pain.[229–231] Previous studies (HALT-PKD studies A and B) showed no association between pain and TKV in people with early disease (CKD G1–G2), except in people with large kidneys (htTKV >1000 ml/m), but pain was more severe in people with late disease (CKD G3b–G4).[230]

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

Identification and resolution of likely causes of chronic kidney in people with ADPKD are critical (Chapter 5). People with refractory chronic kidney or liver pain should be screened for depression. When the pain is refractory and/or complex, it is best managed by a multidisciplinary team[233,234]; the potential therapeutic interventions of such a team are outlined in the pain management infographic below (Figure 15).[235]

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

Shared decision-making between the healthcare provider and the person with ADPKD or that person's caregiver should be applied to the pain management approaches whenever possible, particularly to the more complex decisions and interventions (Figure 15). This process is expected to reduce the patient's anxiety, increase the patient's cooperation, and respect the patient's personal choices and views. Validation, acknowledgment, and in some cases, reassurance often can help to alleviate the anxiety associated with chronic pain.

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

The efficacy and selection criteria of most nonpharmacologic interventions to treat chronic kidney pain in people with 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., with use of the Alexander technique, which is a method for improving posture and movement by identifying and changing harmful habits[236]) have not been systematically evaluated, they may have 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 with pain control.[232] Cognitive–behavioral therapy may be helpful in specific cases. Acupuncture and transcutaneous electrical nerve stimulation (TENS) also may provide relief[232]; however, these options should be reserved for people with pain that is not responsive to nonopioid pharmacologic interventions.

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

Acetaminophen is the first-line drug for chronic pain control. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is discouraged for treatment of chronic pain, but these may be used short-term for acute pain in people with stable kidney function.[237] Tricyclic antidepressants and gabapentin also may be useful as analgesic adjuvants, despite the lack of RCTs in ADPKD.[238] Experience with pregabalin in people with ADPKD is still limited. Tramadol can be used either as a next-line agent or as adjunctive therapy in people with pain that is not appropriately controlled with the previous drugs. Clonidine is an option when acetaminophen and tramadol are not effective or are contraindicated.

Opioids or minimally invasive therapies are options for people with no response to nonopioids or noninvasive therapies (Figure 15). Opioid use should be limited and employed only after failure or inadequacy of all previous approaches has

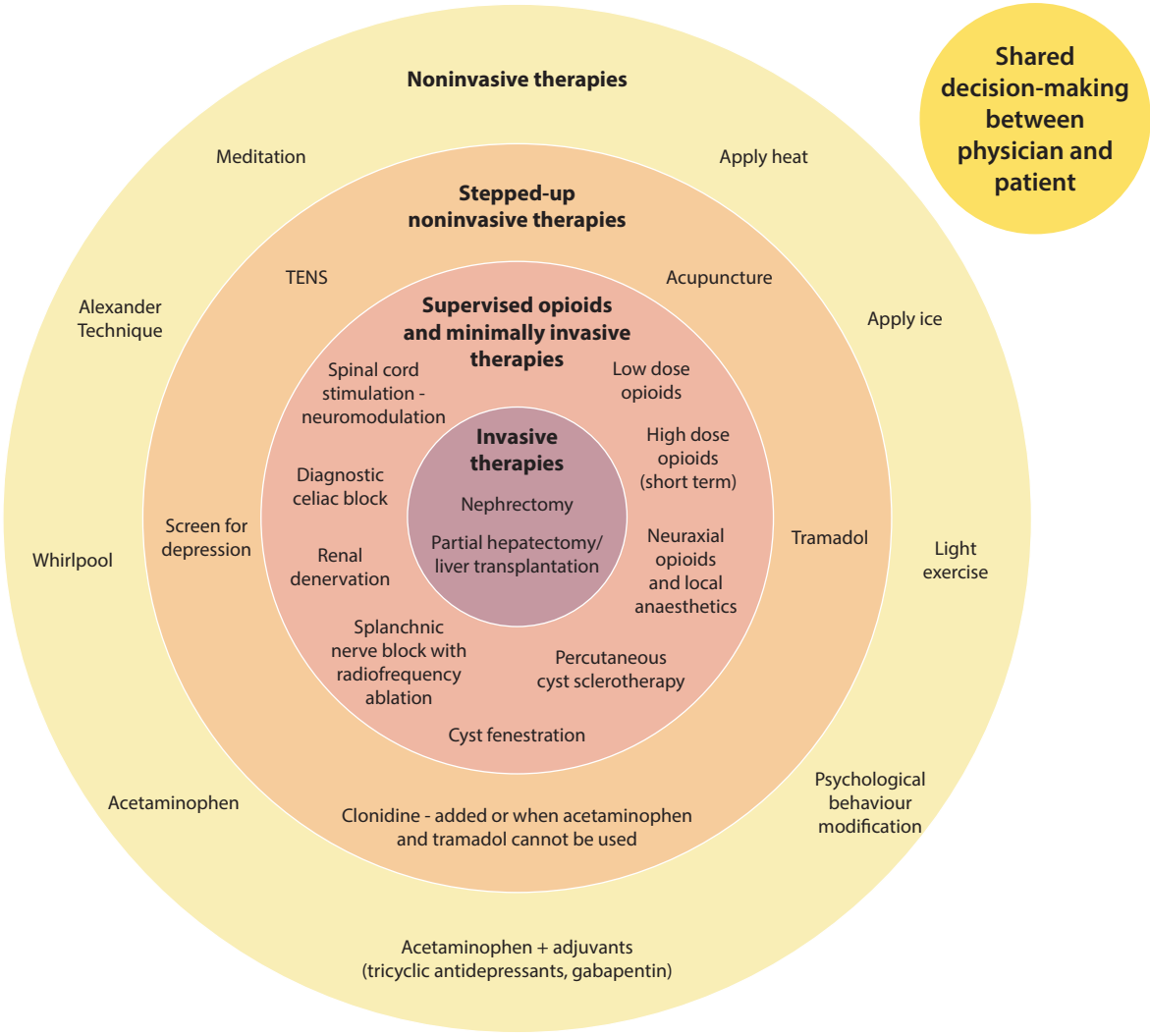


Figure 15 | Shared decision-making in management of chronic kidney pain in autosomal dominant polycystic kidney disease (ADPKD). ADPKD, autosomal dominant polycystic kidney disease; TENS, transcutaneous electrical nerve stimulation. The size of each concentric circle denotes how widely the treatment or maneuver may be used (i.e., treatments within the largest circle should be widely used, whereas those within the smallest circle should be used rarely).

been demonstrated. If high-dose opioids are required to appropriately relieve pain, their usage should be 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. Opioid use for chronic pain management is associated with a high risk for addiction, responsible for the current opioid epidemic in many countries, and should therefore be pursued with great care.[239] 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 people with ADPKD depend on cyst characteristics and on the local expertise of the surgeon/interventional radiologist. Referral to a center of expertise should be made whenever possible.

A sequential approach to making choices among the range of minimally invasive to invasive interventions for chronic kidney pain in people with ADPKD is proposed in Figure 15. The proposed sequence and choices of procedures, however, assumes the availability of all required interventional expertise. Given that such expertise is not universally available, the sequential approach can vary widely among centers and countries. Thus, the 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 centers.

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.[232,240] Percutaneous cyst aspiration, coupled with injection of a sclerosant to ablate the cystic lining (i.e., sclerotherapy), or laparoscopic cyst fenestration and/or decortication may lead to long-lasting pain control.[241] Foam sclerotherapy or laparoscopic cyst fenestration usually are employed in people with large (>5 cm) accessible kidney cysts that cause significant "mass effect" symptoms (e.g., abdominal pain and distention, early satiety, and heartburn due to acid reflux).[240,242–244] Which choice is adopted depends highly 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 in providing 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.[231] 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 majority of the 44 people included in the study had a sustained decrease in pain intensity after a median follow-up of 12 months.[231] Another small study ($n = 11$) suggests that percutaneous catheter-based renal denervation reduces pain complaints and the use of analgesics in people with ADPKD.[245]

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.

Although spinal-cord stimulation may lead to marked pain control in specific cases of moderate-to-severe refractory mechanical or visceral pain, a point that must be noted is that, depending on the implanted device, it may preclude the performance of MRI studies. This concern is based mainly on the potential for heating of the generator and/or the 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.[229] Laparoscopic nephrectomy usually is preferred over open surgery, as it is associated with a 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.[246]

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 (Figure 15).[234]

Research recommendations

- Epidemiologic studies are needed to define the prevalence of chronic pain associated with PKD and different types of analgesic drug usage.
- Studies are needed to compare the effectiveness of different nonpharmacologic, noninvasive interventions as initial treatment for chronic kidney pain in people with ADPKD.
- Studies are needed to compare the effectiveness of different minimally invasive interventions in people with no response to noninvasive, anti-pain 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 their medical records should be reviewed.

Review of prior history and related records of kidney stones should be included routinely for all people with ADPKD. A significant number of people with ADPKD develop one or more kidney stones during their clinical course.[247] In a recent meta-analysis, the prevalence of kidney stones ranged from 3% to 59% in people with ADPKD, and this range was higher compared to that of their unaffected family members (risk ratio [RR]: 1.8; 95% CI: 1.3–2.6).[248] 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, whereas uric acid stones account for <10% of the cases.[247] However, the frequency of uric acid stones may be increased in people with ADPKD, compared to that in the general population.[247] 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.

Currently, no uniform consensus has been established on the protocol for screening for kidney stones in people with

ADPKD. Many centers routinely screen their patients for kidney stones with the same ultrasound used for the 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.[247]

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

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.[247,249–251] Most people with symptomatic kidney stones have had at least 1 kidney imaging study (typically, a low-dose noncontrasted CT scan) documenting the number, size, and location of their kidney stones. Two 24-hour urine collections for volume, creatinine, sodium, phosphate, potassium, calcium, magnesium, oxalate, citrate, and uric acid, and a spot urine test for urinalysis and pH should be performed to identify any modifiable risk factors. For follow-up, urinary studies should be individualized and repeated at 1 year and periodically thereafter, depending on the activity of stone formation. Additional follow-up kidney imaging should be individualized. Whenever possible, chemical analysis of kidney stone(s) that have been passed or surgically retrieved 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.[252] Although the Work Group agrees with the statements below, this agreement 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).

Adequate water and fluid intake are essential to achieve a urine output of ≥2.5 l/d, which has been shown to lower the risk of kidney stones by 60%–80% in the general population.[253–256] Based on preclinical studies of ADPKD, high levels of water intake may also slow kidney cyst growth by suppressing the central release of arginine vasopressin (AVP), although its clinical effectiveness has not yet been proven.[257,258] A healthy diet rich in fiber, fruits, and vegetables, but low in sodium and animal protein, similar to that recommended for hypertension, obesity, diabetes, and metabolic syndrome, typically is appropriate for people with kidney stones. Additionally, the results of a urinary lithogenic risk profile (i.e., serum for sodium, potassium, calcium, magnesium, phosphate, and uric acid; 24-hour urine collection for sodium, potassium, calcium, magnesium, phosphate, oxalate, uric acid, citrate; and a spot urine test for pH) and stone chemical analyses should be used to guide the treatment.

Assessment by a registered dietitian or accredited nutrition provider is strongly suggested in cases with a history of compromised nutritional status, complex medical situations, or for people who need assistance implementing dietary recommendations. Evidence suggests that people who receive specific dietary recommendations based on a comprehensive evaluation have fewer stone recurrences over a 3-year period than do those who receive only general dietary advice.[259]

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.

In general, depending on the level of the ureteric obstruction (proximal, mid-, or distal) and the size of the stone (>10 mm or <10 mm), extracorporeal shock-wave lithotripsy or ureteroscopy may be the preferred first-line treatment, whereas percutaneous nephrostomy generally is considered as a second-line intervention. The presence of large kidney cysts may make extracorporeal shock-wave lithotripsy or percutaneous nephrostomy more difficult to perform. The results of these interventions in treating obstructing stones are highly variable among centers and procedure types.[260]

Research recommendations

- Study of the effectiveness of asymptomatic kidney-stone screening strategies is needed for people with ADPKD (e.g., using the same ultrasound for the first diagnosis of ADPKD vs. a dedicated, low-dose, noncontrasted CT scan). This study also requires more accurate estimates of the prevalence of symptomatic and asymptomatic kidney stones in people with ADPKD.
- The relative contributions of anatomic and metabolic factors for stone formation in people with ADPKD are unclear. A better understanding of pathogenesis is required for effective pharmacologic prevention and treatment strategies.

2.4 Gout

Currently, no evidence indicates that the prevalence of gout is greater in people with ADPKD. However, gout is prevalent in the general population and is more common in people with CKD; therefore, gout management is a concern for people with ADPKD.[261]

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.[262] Although the Work Group agrees with the statements below, this agreement 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 (540 μmol/l), or urolithiasis, we conditionally recommend initiating ULT.

Recommendation 2.4.3: For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl or 408 μmol/l 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/d [and lower in patients with CKD] for allopurinol or ≤40 mg/d 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.

Practice Point 2.4.1: People with ADPKD should not be treated pharmacologically for asymptomatic hyperuricemia. However, lifestyle and dietary modification may be beneficial (see *2020 American College of Rheumatology Guideline for the Management of Gout*[262]).

The above statements for management of gout have been recommended for the general population but should be equally valid for people with ADPKD. These statements apply to all people and are not specific to people with CKD or ADPKD.

The Work Group agrees with the *2020 American College of Rheumatology Guideline for the Management of Gout*.[262] Currently, no evidence indicates that ADPKD is associated with hyperuricemia or that medical treatment of hyperuricemia slows the progression of ADPKD.[160]

However, as for the general population, if a person presents with a diagnosis of asymptomatic hyperuricemia, counseling is appropriate 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.[262] 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.[160] Use of diuretics was not associated with hyperuricemia in the HALT-PKD study.[160]

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

The Work Group agrees with the *2020 American College of Rheumatology Guideline for the Management of Gout*, which recommends prescribing urate-lowering medications for people with gout and subcutaneous tophi, radiologic evidence of joint destruction attributable to gout, or ≥2 gout attacks per year.[160,262] Allopurinol is recommended as the preferred first-line agent, including for 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/d), close monitoring for adverse effects, and slow uptitration of the allopurinol dose (by 50–100 mg/d every 4 weeks).[263] Providing anti-inflammatory prophylaxis for 3–6 months (e.g., colchicine 0.6 mg/d for CKD G1–G3, 0.3 mg/d 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.[262,263]

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 people with these backgrounds, 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.[262,263]

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 *UMOD*, *MUC1*, or *HNF1B* mutations, which are causes of ADTKD (also see Chapter 1).[16] Of people with *UMOD* mutations, 30%–40% have kidney cysts, usually distributed in the kidney medulla and not causing enlarged kidneys, which can be misdiagnosed as ADPKD, especially in younger people.[95]

2.5 Hematuria

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

Gross hematuria is a common clinical finding that is often distressing to people with ADPKD.[232,233,264,265] A precipitating event, such as physical trauma to the abdomen or strenuous activity, occasionally can be identified; however, most episodes occur spontaneously. Spontaneous hematuria is more likely to occur among people with larger kidneys, hypertension, and advanced stages of CKD.[242] Early-onset (i.e., at ages <30 years) gross hematuria is associated with more rapid progression of kidney disease in people with ADPKD.[170]

Cyst hemorrhage and rupture into the collecting system are 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, as many cysts do not communicate with the collecting system.[264] 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 NSAIDs, 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.[266] The antifibrinolytic agent tranexamic acid has been used in small series and case reports of people with ADPKD and severe gross hematuria or kidney hemorrhage, but the possible benefit needs to be balanced with an increased risk of urinary tract obstruction due to clotting, and of thromboembolic events. 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: Healthcare providers should discuss the possibility of gross hematuria with patients at the time of diagnosis of ADPKD to avoid unnecessary worry if it happens.

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 1 or 2 days. In this case, immediate medical attention may not be necessary, but patients should increase their 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. Such an occurrence 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, avoiding contact sports in which blunt trauma to the kidney is possible may be prudent.

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.[268] Although 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 people with ADPKD and does not necessarily indicate a UTI.[267] Asymptomatic pyuria and asymptomatic bacteriuria should not be treated with antibiotics (except during pregnancy), which is the same recommendation as that for the general population.[268] For documented bacterial cystitis, antibiotics such as

nitrofurantoin, TMP-SMX, 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 (aged >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 (resulting in 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. 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: A urine culture should be obtained before antibiotics are started for UTI, especially for upper UTI and/or suspected kidney cyst infection. Blood cultures should be obtained if an upper UTI or kidney cyst infection is suspected.

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) measurement, blood and urine cultures, urinalysis, and abdominal imaging. The presence of fever, abdominal or flank pain, elevated white blood cell counts, and elevated 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 16).

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 (because they typically cannot differentiate between blood and 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 ^{18}F-fluorodeoxyglucose integrated with positron emission tomography/computed tomography (^{18}F-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 16).[269]

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

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

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 that the cyst infection is adequately addressed. This recommendation places a low value on the costs and side effects of this approach. The recommendation is Level 2 because although it is widely accepted by the clinical community, the grade of certainty of evidence is very low at the present time.

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 a longer duration of antibiotic treatment, due to the poor penetration into cyst fluid that occurs with most antibiotics (except those with lipophilic properties). Additionally, establishing a firm clinical diagnosis of kidney cyst infection may be difficult. Thus, 4–6 weeks of empirical treatment with a lipophilic antibiotic that covers common urinary pathogens generally is 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.

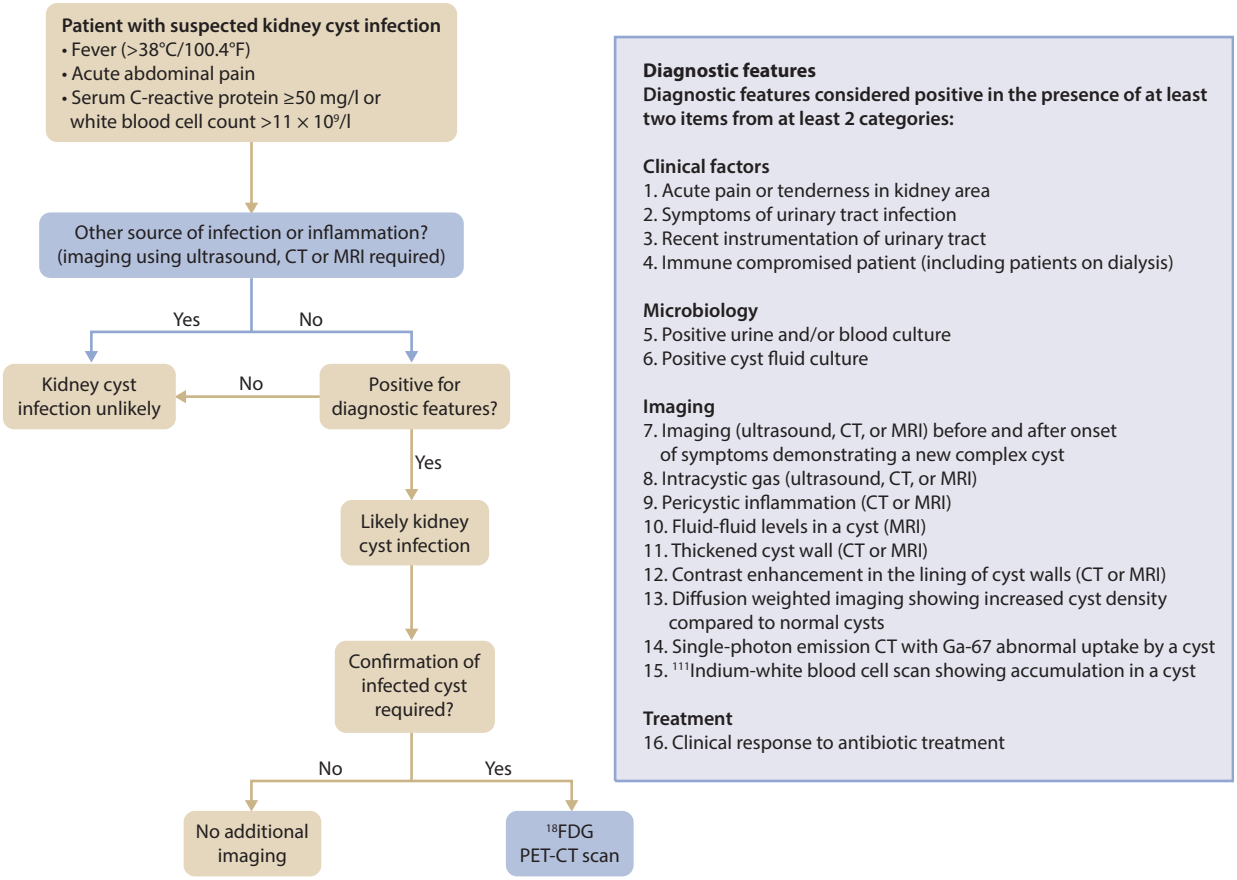


Figure 16| Diagnostic algorithm for an infected kidney cyst in autosomal dominant polycystic kidney disease. CT, computed tomography; ^{18}FDG PET-CT, positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with computed tomography; Ga-67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga *et al.*[269]

Certainty of evidence. No systematic reviews or comparative studies have evaluated the optimal duration of antibiotic treatment for people with ADPKD and kidney cyst infection. The current recommendation is based on expert opinion with a very low grade of certainty of evidence.

Values and preferences. This recommendation places a high value on the seriousness of a 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 that taking 6 weeks of antibiotics is challenging or unacceptable. In this situation, shared decision-making between the person with ADPKD and that person's healthcare provider, preferably with the input of an infectious disease specialist, is essential.

Resource use and costs. The costs of oral antibiotics (e.g., fluoroquinolone or TMP-SMX) used for cyst infection are modest. However, other antibiotics that require i.v. administration may be prescribed in the occasional case of an infected cyst because of 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 usually is not an issue. However, in the occasional case of a person in whom i.v. antibiotic treatment is required, additional resources (i.e., a home nursing visit for administration of an 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 TMP-SMX, 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) indicating that prolonged use of this class of antibiotics may be associated with increased risks of aortic aneurysm and dissection, based on clinical and experimental studies.[270,271]

The incidence of pyelonephritis leading to a cyst infection is not unusual. Given that differentiating between the 2 diagnoses is difficult, and that both may be present simultaneously, a conservative approach would be to treat upper UTI for 4–6 weeks, unless a clear indication is present 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 process 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 people with ADPKD, by geographic 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: There is no clear association between ADPKD and an increased risk of renal cell carcinoma (RCC).

RCC is an infrequently documented complication 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 ($n = 4346$) ADPKD showed an increased kidney-cancer risk (adjusted HR: 2.45; 95% CI: 1.2–4.65) in people with ADPKD.[272] By contrast, 2 smaller registry studies of people with kidney failure or kidney transplant did not show an increased risk of RCC in people with ADPKD, compared to the risk of other chronic kidney diseases.[273]

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

RCC in people with ADPKD, compared to that in the general population, more frequently presents with fever (32% vs. 7%), as bilateral (12% vs. 1%–5%) and multicentric (28% vs. 6%) disease, and it more often displays sarcomatoid features (33% vs. 1%–5%).[274] Clinical findings such as hematuria, flank mass, and complex cystic kidney lesions, all of which are common in people with ADPKD, may confound and delay 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 another obvious explanation, or documentation of a rapidly growing complex cystic kidney lesion, should raise the suspicion of RCC.[274] Contrast CT or MRI are often able to distinguish malignancy from complex cysts due to hemorrhage; percutaneous aspiration, and cytologic examination of 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 that in 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 pretransplant screening for RCC improves outcomes for people with ADPKD.

Chapter 3: Chronic kidney disease (CKD) management and progression, kidney failure, and kidney replacement therapy (KRT)

3.1 CKD management and progression

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

Management of CKD has been reviewed extensively in prior KDIGO guidelines.[215,216,237,275–277] People with ADPKD should be treated using the same recommended management guidance as that for those with CKD, unless otherwise specified in this chapter.

General measures relevant for CKD management in people with ADPKD are discussed in specific chapters or practice points of this guideline, as indicated in Figure 17.

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

People with ADPKD tend to have a higher hemoglobin level, compared to that of people with other forms of CKD,[278] 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.[279] Erythrocytosis (hematocrit >51% or hemoglobin >17 g/dl [170 g/l]) may occur in people with ADPKD, rarely before kidney failure, and more frequently following kidney transplantation (see Practice Point 3.2.1). 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.

Measure	Refer to the following:
Blood pressure control	Chapter 2
Use of organ protective therapies	Chapter 2 and Chapter 4
Dietary sodium intake	Chapter 1, 2, 4, and 7
Regular exercise	Chapter 7
Dietary protein intake	Chapter 7
Management of anemia	Practice Point 3.1.2.
Management of diabetes	Practice Point 3.1.4.

Figure 17 | Measures for chronic kidney disease management in people with autosomal dominant polycystic kidney disease, with reference to specific sections of the guideline.

Please refer to the *KDIGO Clinical Practice Guideline for Anemia in CKD* for specific guidance.[276]

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

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.[280] In an experimental mouse model of ADPKD, HIF-PHI resulted in severe aggravation of the phenotype with rapid loss of kidney function.[281] HIF-1α also may promote cyst growth in polycystic livers.[282] The evidence is limited regarding the benefits and harms of HIF-PHI in people with ADPKD.[283]

In a study of roxadustat in people with CKD who are receiving dialysis,[284] 7.3% of participants had PKD. In these people, no kidney cyst–related complications were reported, but these were not specifically assessed.[285] The incidence of treatment-emergent adverse events due to kidney cysts was less than 1% in 594 people with CKD not receiving dialysis, of which about 10% had PKD; however, no specific monitoring of kidney cyst growth or complications was conducted.[286]

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

As in the general population, type 2 diabetes is highly prevalent among people with ADPKD. Therefore, ADPKD and type 2 diabetes frequently coexist. People with ADPKD and type 2 diabetes have been shown to have kidney volumes almost 2-fold larger than those of matched people with ADPKD without diabetes.[287] 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*.[288] Hyperglycemia aggravates cell proliferation and cyst formation in a mouse model of PKD induced by the deletion of the intraflagellar transport protein Ift88.[289] Increasing evidence from preclinical animal models suggests that metabolic defects likely contribute to the pathogenesis of ADPKD.[290]

The statements in the *KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* are applicable to people with ADPKD, with the possible exception of recommendations for the use of SGLT2i.[216]

There is no clear evidence of specific benefits or harms from diabetic therapies in people with ADPKD with or without type 2 diabetes, 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. However, use of SGLT2i in ADPKD is not presently recommended, because people with ADPKD have been excluded from the clinical trials; thus, its safety has not been evaluated. Although the renal hemodynamic effects of SGLT2i (stimulating tubuloglomerular feedback, and lowering glomerular hypertension and hyperfiltration) and their metabolic effects (like those of caloric restriction) may be protective in ADPKD, because of osmotic diuresis, SGLT2i increase the release of vasopressin, which may promote cyst growth. 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 that in controls.[291] 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 an eGFR of 30–90 ml/min per 1.73 m^2. The use of SGLT2i after kidney transplantation, in general, has been limited by concerns of infection and has not been evaluated specifically in post-transplant people with ADPKD.[292] The opinion of the Work Group is that, at the moment, the only potential justification for using SGLT2i in people with ADPKD is the presence of heart failure.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are thought to be kidney-protective, by lowering glucose and lipid levels, weight, BP, and inflammation level. No clinical trials in people with CKD or ADPKD without diabetes, nor preclinical studies in rodent models of ADPKD using GLP-1 RAs have been performed.

The evidence is limited that suggests that thiazolidinediones (pioglitazone and rosiglitazone) may be safe to use in people with ADPKD. 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 of slowing kidney growth or leading to eGFR decline.[293] 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.[294–296]

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*.[277]

Lipid management in CKD was comprehensively reviewed in the *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease*.[277] Although no studies demonstrating a lipid-lowering benefit have been conducted specifically in people with ADPKD, reduced eGFR and albuminuria are strongly associated with cardiovascular morbidity and mortality. Lipid-lowering therapy reduces the incidence of 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*.[297,298]

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 level <55 mg/dl [<1.4 mmol/l]) for primary protection in people with CKD not on dialysis.[299] However, due to concerns regarding safety and tolerability of using high-intensity statins in CKD, the Work Group agrees with the adoption of *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease* in people with ADPKD (Figure 18).[277] The KDIGO Work Group did not recommend the treat-to-target strategy, because it had never been proven to be 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 *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.

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

Development of new or improved therapeutic interventions to slow the progression of ADPKD requires the performance of RCTs. Healthcare providers should notify people with ADPKD about the availability of clinical trials for which they might be eligible. Such information should be provided in a neutral fashion, with full opportunity for people to determine whether participation in a particular trial is feasible for their own circumstances.

Research recommendations

- Studies are needed to assess the impact of new glucose-lowering therapies, such as SGLT2i and GLP-1 RAs, and of biguanides and thiazolidinediones on the progression and complications of ADPKD.
- Studies are needed to determine whether enhanced glycemic control in people with ADPKD and diabetes slows progression.

Recommendation
In adults aged >50 years with CKD and eGFR >60 ml/min/1.73 m^2 (GFR categories G1–G2) we recommend treatment with a statin (1B).
In adults aged >50 years with eGFR <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).
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 >10%
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).

Figure 18 | Recommendations from the *KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease*.[277] CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

- Studies are needed to assess the role of erythropoiesis-stimulating agents, including hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) in the treatment of anemia associated with ADPKD. Exploratory subanalyses of major HIF-PHI trials are needed to compare the kidney function of people with ADPKD versus those with other forms of CKD.
- Studies are needed to determine how to increase clinical trial participation by people with ADPKD.

3.2 Kidney transplantation

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

People with ADPKD generally do well after transplantation, reflecting the nature of the disease. Outcomes are comparable to those in the general transplantation population and typically are better than those of people with diabetic nephropathy. Thus, kidney transplantation is the preferred management option for people with ADPKD and kidney failure.[300,301]

The principal cause of mortality in all forms of kidney failure is CVD. In an analysis of mortality in a large cohort from the U.S. 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.[301] Nevertheless, a number of post-transplant complications specific to ADPKD have been reported (Figure 19). Some of these complications, such as erythrocytosis or cardiac valvular disease, reflect an ongoing progression of conditions associated with ADPKD that existed prior to transplantation.[302–307] Administration of an ACEi or an ARB is usually the initial treatment for post-transplant erythrocytosis, with hematocrit and hemoglobin targets of <51% and <17 g/dl (170 g/l), respectively. Therapeutic phlebotomy is indicated when an ACEi or an ARB is contraindicated or is ineffective at a maximal-tolerated dose. Exceptionally, bilateral nephrectomy can be considered in people with ADPKD, kidney failure, and resistant erythrocytosis. Increased awareness of these issues, and vigilant screening and management, are required. Currently, the evidence does not support assessing post-transplant people with ADPKD for osteoporosis differently from post-transplant people with other chronic kidney diseases

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

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

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

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

Provision of a living-donor transplant allows the elective performance of the transplant when the recipient has 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*

Post-transplant complication	
New-onset diabetes	Pooled RR 1.92; 95% CI: 1.36–2.70[a]
Erythrocytosis	Recipients with post-transplant erythrocytosis were more likely to have PKD than other kidney diseases (17% vs. 6%; P <0.001)[b]
Valvular heart disease	Greater risk for worsening of tricuspid, mitral and aortic valve regurgitation[c]
Aortic root dilatation	Greater risk for dilation of sinus of Valsalva and ascending thoracic aorta[d]
Subarachnoid hemorrhage	3.8/1000 hospital admission in kidney transplant recipients with ADPKD compared to 0.9/1000 in kidney transplant recipients without ADPKD[d]
Thromboembolic events (DVT, PE)	8.6% of 534 patients with ADPKD vs. 5.8% of 4779 patients without ADPKD after kidney transplantation ($P = 0.009$)[e]
Skin cancers: SCC, BCC, melanoma	Adjusted ORs 1.22, 1.30, 1.21, respectively[f]
Urinary tract infections	Weak evidence only
Cyst infection	Cumulative IR 3%, 6 % and 12% (63% kidney, 37% liver) at 1, 5 and 10 years after transplantation (1.6 episodes per 100 person-years). Increased risk with history of cyst infection before transplantation, HR: 3.47; 95% CI: 1.29–9.31[g]
Colon diverticulitis	Prevalence (2006–2013) in kidney transplant recipients with compared to without ADPKD (2.6% vs 0.8%)[h]

Figure 19| Post-transplant complications that are more common with autosomal dominant polycystic kidney disease (ADPKD) than they are in people with other forms of chronic kidney disease (CKD). BCC, basal cell carcinoma; CI, confidence interval; DVT, deep vein thrombosis; IR, incidence rate; HR, hazard ratio; OR, odds ratio; PE, pulmonary embolism; PKD, polycystic kidney disease; RR, relative risk; SCC, squamous cell carcinoma. [a]Cheungpasitporn *et al.*[308]; [b]Alasfar *et al.*[309], Alzoubi *et al.*[310], Jacquet *et al.*[311], Mekraksakit *et al.*[312], and Ronsin *et al.*[313]; [c]Chedid *et al.*[314]; [d]Cheungpasitporn *et al.*[315]; [e]Jacquet *et al.*[311]; [f]Hao *et al.*[316]; [g]Ronsin *et al.*[313]; [h]Duarte-Chavez *et al.*[317]

Practice Guideline on the Evaluation and Care of Living Kidney Donors[318]).[307,319,320] 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).[318] 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 depend 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, evaluation of the extended family has value, and of the wider circle of friends, coworkers, and acquaintances, within the limits specified by each country. From the patient perspective, the preferable approach is for the physician to educate the patient about the benefits of evaluation of both family and other potential donors, so that patients can develop an outreach plan that fits within their own and their family's values and culture. Patients must understand that it is to their benefit to find a living donor, which offers the best outcome if the point of kidney failure is ever reached. If a person is diagnosed later in life and/or with declining eGFR, this conversation can occur at a point as early as the initial diagnosis, because this is when patients are 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. Such discussions also could include education regarding healthier donor lifestyles, including weight reduction, smoking cessation, a heart-healthy diet, and behaviors to facilitate the candidacy of potential kidney donors. (For more details, please refer to *KDIGO Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors*[321]) Such evaluations will facilitate the education of potential kidney donors and transplant candidates about the options, risks, and benefits of living-donor kidney transplantation.

The performance of blood type– or human leukocyte antigen (HLA)–incompatible living-donor kidney transplantations can be facilitated via enhanced immunosuppression or kidney exchanges of 2 or more donor–recipient pairs, including altruistic donors in some countries. Timing and organization of such exchanges are managed by transplantation centers and organ-procurement organizations.[318,322,323]

No convincing evidences supports that people needing a transplant because of ADPKD have a different benefit or risk profile than do those who have other forms of CKD. One study suggests that sirolimus has a benefit in reducing the growth of polycystic livers after transplantation.[324] An analysis of a limited number of people with a kidney transplant

$$\text{Adjusted BMI (ADPKD)} = \frac{\text{Adjusted body weight (kg)}^*}{\text{Height (m)}^2}$$

$$^*\text{Adjusted body weight} = \text{Measured body weight (kg)} - \text{TKV (in kg)} - \text{TLV (in kg)} + \text{weight of normal kidneys (kg)}^\dagger \text{ and liver (kg)}^\dagger$$

Figure 20 | Calculations for adjusted body mass index (BMI) in people with autosomal dominant polycystic kidney disease (ADPKD). TKV, total kidney volume; TLV, total liver volume. *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; 1 liter of volume is assumed to equal 1 kg of weight. Normal kidney and liver weights vary with age and BMI (https://pathology.oit.duke.edu/siteParts/Typical%20Organ%20Weights.pdf). †A reasonable approximation for total kidney weight is 0.27 kg for men and 0.23 kg for women; for liver, a reasonable approximation is 1.6 kg for men and 1.3 kg for women.

and ADPKD showed that cystic-kidney volumes regressed significantly more on a sirolimus-based regimen than they did on a calcineurin inhibitor–based immunosuppressive regimen. RCTs of mammalian target of rapamycin (mTOR) inhibitors in people with ADPKD without a transplant mostly have been ineffective in slowing progression (Chapter 4).[325]

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

Chapter 1 presents the guidance to use to establish or exclude a diagnosis of ADPKD. Ultrasound can generally be used for the initial screening, as 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 3.2.7: During the pretransplantation work-up for candidates with ADPKD, the total kidney and liver weight derived from total kidney and liver volumes should be calculated and subtracted from the patient's total body weight for a more accurate assessment of weight and body mass index (BMI).

Given that end-stage ADPKD can result in up to 18 kg (40 pounds) 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 estimated kidney and liver weights should be subtracted from a patient's total weight to arrive at a more accurate indication of patient health (Figure 20). This calculation assumes that 1 ml of kidney or liver volume is equivalent to 1 g of weight. Skinfold caliper measurements also can be used to estimate BMI.

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

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

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 Level 2 in the opinion of the Work Group because of the low grade of certainty of evidence demonstrating no benefit of the procedure, with limited concerns for safety associated with nephrectomy in people with ADPKD.

Key information

Balance of benefits and harms. The evidence review found 9 studies that compared people with ADPKD who had nephrectomy with those who did not.[326–335] 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

- Recurrent and/or severe kidney infection
- Symptomatic nephrolithiasis
- Recurrent and/or severe kidney cyst bleeding
- Intractable pain
- Suspicion of kidney cancer
- Insufficient space for insertion of a kidney graft
- Ventral hernia in the setting of massively enlarged kidneys
- Severe symptoms related to massively enlarged kidneys*

Figure 21 | Potential indications for native nephrectomy in people with autosomal dominant polycystic kidney disease receiving a kidney transplant. *People with chronic kidney disease should be asked for pain- and volume-related complaints in a structured manner.

conducted at the time of transplantation.[329] One small study reported a decreased frequency of kidney cyst infection and of persistent hypertension among those undergoing nephrectomy for ADPKD at the time of kidney transplantation,[327] but these outcomes were not reported by other studies. However, in some situations, native nephrectomy may be warranted, including those involving pain, bleeding, nephrolithiasis, infection, suspected cancer, etc. (Figure 21). The indication also may determine the timing of the nephrectomy. For example, nephrectomy for a suspected cancer, or after a recent infection, should be performed before transplantation.

Certainty of evidence. The overall grade of 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 S9[326–336]). The lack of adjustment (or randomization) was of particular concern in these studies, in which the likelihood is high that numerous inherent differences will be present between those patients and healthcare providers who choose nephrectomy and those who do not. This concern resulted in a low grade of certainty of evidence regarding the outcomes critical for decision-making, graft loss, and long-term all-cause mortality, and the important outcome of delayed graft function. Only single small studies reported several critical outcomes, precluding the drawing of conclusions. The critical outcomes of allograft function, quality of life (QoL), and RCC (in the native kidney), and the important outcome of cyst infections (in the native kidney) were reported by single small studies with serious methodological limitations, thus yielding a very low grade of 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, a very low grade of certainty of evidence; however, a large study, with some (not serious) limitations, provided a low grade of certainty of evidence regarding the risk of requiring a blood transfusion. Studies did not report outcomes for numerous critical and important outcomes. Based primarily on the low grade of certainty of evidence for the critical outcomes of graft loss and death, together with the low grade of certainty of evidence for the surgical complication of transfusion, we concluded that overall, the grade of certainty of evidence is low.

Values and preferences. The choice to proceed with an invasive surgical procedure requires careful consideration by all parties involved. This recommendation places a relatively higher value on avoiding procedures that do not have clearly identifiable clinical or patient benefit. Although we recommend not undertaking 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 Level 2, as the Work Group judged that the majority of well informed people would not choose to undertake routine native nephrectomy and would consider it only if a specific or compelling indication to do so was present.

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 relevant team members and the patient should be convened in circumstances in which native nephrectomy is being considered for a person affected by ADPKD.

Healthcare providers 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 often will enter the nephrectomy discussion being in favor of the procedure. During this discussion, an important point on which physicians and/or surgeons should educate patients is that native ADPKD kidneys commonly shrink up to 30% in the first year after transplantation, which may impact many side effects that people experience.[337,338]

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 at up to 1 year postoperation. No identifiable benefit was present for any of the efficacy outcomes, even though no apparent increase occurred 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 arise clinically in which nephrectomy may be considered in the context of potential surgical complications (Figure 22).

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

This recommendation places a high value on the relative absence of evidence to guide the making of any specific recommendation for or against bilateral, as opposed to unilateral, nephrectomy, with experience indicating that healthcare providers exercise great caution and consideration in such a context, if clinically indicated. The recommendation is Level 2 because of the very low grade of certainty or lack of evidence addressing the comparison of bilateral versus 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.[246] The only information relevant to this recommendation was that regarding surgical complications, which did not indicate clear excess complications of bilateral versus unilateral nephrectomy, although this

Operative complications (hemorrhage, infection, pneumonia, wound infection, bowel perforation, rarely death)
Loss of excretory capacity/residual kidney function
Loss of erythropoietic function
Increased sensitization if blood transfusions required
Hemodynamic instability
Fluid retention due to loss/reduction of urine output
Inadvertent adrenalectomy

Figure 22 | Potential complications of native nephrectomy in autosomal dominant polycystic kidney disease.

incidence is likely limited by cohort size, rather than reflecting true noninferiority. Given the lack of evidence to support the benefit of bilateral over unilateral nephrectomy, the Work Group recommends the unilateral nephrectomy surgery to minimize the risk of complications or negative patient outcomes from the more invasive bilateral nephrectomy. Additional risks may be present with bilateral nephrectomy, such as refractory postoperative hypotension. However, in exceptional situations, bilateral nephrectomy may be warranted, including infection, nephrolithiasis, bleeding, pain, suspected cancer, etc. (Figure 21).

Certainty of evidence. The overall certainty of evidence was graded as very low (Supplementary Table S10[246,336]). Only a single, small study provided separate data for people undergoing either bilateral or unilateral surgery, but the study primarily compared hand-assisted laparoscopic nephrectomy with open nephrectomy, with separately reported data for bilateral or unilateral nephrectomies. Thus, serious limitations were present regarding the comparison of bilateral versus unilateral nephrectomy. The study reported only surgical complications, which had a very imprecise effect size estimate. Therefore, the grade of certainty of evidence was low. The certainty of evidence was also graded as very low for surgical complications.

Values and preferences. The choice to proceed with an invasive surgical procedure requires careful consideration by all parties involved, and the Work Group suggests that such consideration is especially important in the case of 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 a greater incidence of complications in one or the other procedure. Consequently, the Work Group advises 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 Level 2, 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 consider it only if a specific or compelling indication to do so was present.

Resource use and costs. All surgical procedures entail health service utilization, with impacts regarding 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 needs to be discussed transparently in each individual instance.

Considerations for implementation. A multidisciplinary discussion involving all relevant team members, in addition to incorporating the patient's perspectives, should be convened in circumstances in which native 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 on the Work Group concern about potential increased complications from performing bilateral nephrectomy. This concern persisted, despite a single study that reached uncertain conclusions about the benefits and complications. This study indicated that bilateral nephrectomy technically can be performed, rather than unilateral nephrectomy, for people affected by ADPKD, although the benefits and complications are insufficiently clear. On balance, the absence of benefit in the presence of any surgical complication had some impact in guiding the rationale of this recommendation, but the Work Group recognized that alternate and individual scenarios may arise clinically in which bilateral, rather than unilateral, nephrectomy may be considered in the context of potential surgical complications.

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

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

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 on the comparable surgical complications associated with the timing of nephrectomy. The recommendation is Level 2 because of the low grade of 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).[333] 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 near-significant association of pretransplant nephrectomy with an 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 they are not addressed in these studies.

Although no evidence indicates an association of excess risk of mortality or major complications with the undertaking of native nephrectomy at the same time as kidney transplantation in ADPKD, additional aspects should be taken into consideration. Factors such as a longer operative time and an increased risk of blood transfusions have been noted.[339] These likely have a role to play in personalized and shared decision-making, with nonsynchronous native nephrectomy being one strategy to minimize the risk and likelihood of them being experienced.

Certainty of evidence. The overall certainty of evidence was graded as low, due primarily to the methodological limitations of the mostly retrospective, unadjusted analyses for critical outcomes of interest (Supplementary Table S11[326,330,331,333,340–343]). The lack of adjustment (or randomization) was of particular concern in these studies, as they carry a high likelihood of numerous inherent differences among patients and healthcare providers who choose different timing for nephrectomy, and possible differences in the experience of the surgeons who conduct the various surgeries. This concern resulted in a low grade of 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 of graft loss and the important outcomes of major surgical complications (except for surgical death). For the critical outcome of surgical death (Clavien-Dindo category V), the effect size estimated was based primarily on one large study (with some methodological limitations; a second, small, highly imprecise study also was conducted). Thus, we determined that the evidence was sparse (based on a single study), yielding a low grade of certainty of evidence. This large study similarly provided a low grade of certainty of evidence regarding the important outcome of risk of transfusion at the time of transplantation. Primarily because of limited data reporting on allograft function from studies with serious methodological limitations, the grade of certainty of evidence was very low for the critical outcome. A single small study with serious methodological limitations provided a very low grade of certainty regarding the important outcome of delayed graft function. Studies did not report outcomes for numerous critical and important outcomes. Based primarily on the low grade of certainty of evidence for the critical outcome of death (both long-term and post-transplant), together with the low grade of certainty of evidence for the surgical complication of transfusion, we concluded that overall, the grade of certainty of evidence is low.

Values and preferences. Planning for and choosing to undertake an invasive surgical procedure requires careful consideration. This recommendation places a relatively higher value on the potentially improved all-cause and in-hospital mortality benefits in cases in which nephrectomy is undertaken with or after kidney transplantation for ADPKD. The recommendation also places a low value on the comparable surgical complications associated with the timing of nephrectomy. We reiterate the earlier recommendations to not undertake nephrectomy as a routine procedure for the majority of people with ADPKD without a specific indication, and to undertake careful multidisciplinary discussion if nephrectomy is being considered. The recommendation is Level 2, as the Work Group judged that most well informed people would not choose to undertake routine native 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 has 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 in which native nephrectomy is being considered for a person affected by ADPKD. The experience of the surgical team needs to be taken into consideration.

Rationale

This recommendation was based on a systematic review of 7 studies that examined all-cause mortality, graft loss, delayed graft function at >1 year, and surgical complications. No clear benefit in outcomes occurred. One large database analysis suggested that the risk of in-hospital mortality at the time of transplantation with pretransplant nephrectomy is increased, but overall, studies found no apparent increase in other major surgical complications. A trend toward improved all-cause mortality was present when nephrectomy was undertaken with or after kidney transplantation, rather than before, in people with ADPKD. 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 arise clinically in which nephrectomy consideration may be required in the context of potential surgical complications. The expertise and experience of the surgical team also are critical to decision-making regarding whether to perform native nephrectomy for people with ADPKD, and its timing in relation to transplantation.

Recommendation 3.2.4: When feasible, we suggest the use of hand-assisted 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-assisted laparoscopic nephrectomy, and it places a low value on the lack of clinical benefit of various surgical approaches to nephrectomy in ADPKD. The recommendation is Level 2 because of the low grade of certainty of evidence addressing all identified surgical complications, and the 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-assisted laparoscopic nephrectomy to open nephrectomy in people with ADPKD.[246,344,345] None of these studies demonstrated clear benefit in terms of either all the combined or the differing Clavien-Dindo grades of surgical complications; however, hand-assisted 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, due primarily 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 S12[246,344–346]). The lack of adjustment (or randomization) was of particular concern in these studies, in which the likelihood is high of numerous inherent differences being present among patients and healthcare providers who choose different surgical procedures. Due to low event rates in small studies, the grade of certainty of evidence was very low for the critical outcome of postoperative death and the important outcomes of any surgical complication and of Clavien-Dindo grade ≥IV complication. The effect estimates were more precise for perioperative transfusions, and for Clavien-Dindo grade ≥III complications, allowing a low grade of certainty of evidence for these important outcomes. Given the lack of evidence for outcomes other than surgical complications, and the very low grade of certainty of evidence for the more important surgical complications, we concluded that overall, the grade of certainty of evidence is very low.

Values and preferences. This recommendation places a relatively higher value on the potential that a laparoscopic, rather than an open, surgical procedure is likely to be preferred by many people, owing to its shorter recovery time and improved cosmesis. However, notably, none of the studies comparing surgical techniques addressed this issue. Given that neither surgical approach appears to be inferior to the other in terms of surgical complications, the value of the decrease in transfusion requirements with hand-assisted 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 the earlier recommendations to not undertake nephrectomy as a routine procedure for most people with ADPKD without a specific indication, and to undertake careful multidisciplinary discussion if it is being considered. The recommendation is Level 2, as the Work Group judged that the majority of well informed people would prefer hand-assisted laparoscopic nephrectomy if a specific indication for it was present and the surgical approach was feasible in their particular circumstances.

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. In cases in which it is feasible to perform, 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 in which native nephrectomy is being considered for a person affected by ADPKD. The experience of the surgical team needs to be taken into consideration. The Work

Group recognizes that hand-assisted laparoscopic nephrectomy may not be available universally, due to a lack of surgical experience or necessary equipment.

Rationale

This recommendation was based on a systematic review of 3 studies that examined surgical complications related to hand-assisted laparoscopic, compared with open, nephrectomy. No identifiable difference between approaches occurred, in the various grades of surgical complications, or for all surgical complications combined, although the likelihood of requiring transfusion was decreased. This lower likelihood of transfusion, as well as a less invasive surgical approach, justified this recommendation. The Work Group still recognizes that alternate and individual scenarios may arise clinically in which open nephrectomy may be considered the more appropriate approach.

Kidney embolization has been employed in several centers, as a less invasive alternative to nephrectomy, but it has not been evaluated systematically. Issues similar to those with native nephrectomy, including appropriate timing and loss and/or reduction of excretory function, are present.[347]

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

The risk of significant RCC is thought to not be increased in people with ADPKD receiving dialysis, or who are post-transplant, compared to people with other kidney disease etiologies, in the majority of studies.[273,348,349] Nevertheless, a recent retrospective analysis from Taiwan found an increased likelihood of RCC (25 cases in those with PKD vs. 5 in control subjects [without CKD]; fully adjusted hazard ratio 5.26; 95% CI: 2.01–13.8) in a cohort of people with ADPKD without reduced GFR or kidney failure.[272] Among 79 patients, of whom 50 had kidney failure and were on HD or had been recipients of a transplant for >1 year, 11 of 89 kidneys were diagnosed with carcinoma with a mean diameter of 18 mm.[350] In another study, 16 incidental RCCs were found in 301 native ADPKD kidneys (5.3%).[350,351] Although the approach to screening transplant candidates before or after transplantation has not been standardized, we advise using abdominal MRI to screen for solid kidney lesions within 1 year prior to transplantation. The timing of MRI for a transplant candidate on the deceased-donor waiting list should be based on the anticipated timing of a kidney offer. MRI without i.v. contrast is the appropriate first imaging test for this indication in people with kidney failure, especially if they are dialysis-dependent.[352,353] Although the risk of nephrogenic systemic fibrosis 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 be administered only 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.[354,355] Solid lesions should show more intermediate T1 and T2 signal intensities and can be recognized by their appearance on diffusion-weighted imaging (DWI).[356] If a solid lesion is suspected, based on noncontrast MRI, and it 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 being enhanced, the contrast-enhanced examination provides added value for local tumor staging and evaluation for metastasis. Although contrast-enhanced ultrasound of a target lesion also could be considered, lesion localization and confident visualization with ultrasound often are markedly limited in ADPKD due to kidney size and the multiplicity of cysts.

Research recommendations

- New and ongoing cohort studies and registries of people with ADPKD should analyze outcomes related to native 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, RCTs would be preferred and would provide the strongest evidence.
- Research is needed into the development of objective criteria for determining appropriateness for nephrectomy, including kidney size and symptoms.
- 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 be studied in a systematic fashion.
- 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 their impact on long-term outcomes.
- More evidence is needed regarding the risk of RCC in people with ADPKD receiving dialysis or who are post-transplant, compared to that in 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 who are on dialysis and have a transplant.
- Studies are needed to determine the incidence and severity of kidney-related bleeding complications in people with ADPKD receiving systemic anticoagulation on dialysis or after transplantation.
- Studies should investigate the impact of mTOR inhibitors in slowing the growth of kidney or liver volume after transplantation.

3.3 Kidney replacement therapy

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

If multiple dialysis modalities (in-center HD, home HD, continuous ambulatory, and/or automated PD) are available to a person with ADPKD, a shared decision-making model between the physician and the patient offers the best chance of optimal patient satisfaction. The prescribed dialysis mode ideally is a decision that is personalized based on the underlying health of a particular person, the likelihood of transplantation, caregiver availability, lifestyle, planning for life events, and desire for autonomy. Use of shared decision-making ensures that patients make informed decisions that reflect their values, preferences, and priorities. A lack of shared decision-making often results in a poor level of patient satisfaction with the treatment.[357]

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

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

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

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 Level 2, due to the low grade of 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 of follow-up directly comparing PD and HD in people with ADPKD, and 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 S13[358–361]). 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, no significant differences occurred between people with versus without ADPKD with regard to dialysis dose (Kt/V),[362–364] peritoneal leakage,[363,365,366] peritonitis,[358,361–369] switch to hemodialysis,[358,362–365,369] technique failure,[361–363,366,369] exit-site infection,[363,365] or mortality (Supplementary Table S14[358,359,362–371]).[358,359,361–369] Abdominal hernias were more common in people with ADPKD.[363,365,367,368] The median time to technique failure for those with ADPKD was 6.2 years, versus 6.5 years for those without ADPKD.[362] The median time to death for those with ADPKD was 6.04 years, versus 5.57 years for those without ADPKD.[362] No studies addressed QoL, functional status, psychosocial issues, or pain. No studies provided objective measurements of kidney (and liver) size.

No apparent mortality difference was present between those receiving PD versus those receiving HD. More people switched from PD to HD than from HD to PD, in both the PKD and the non-PKD populations (Supplementary Table S13[358–361]). The incidence of hospitalization for infection in people receiving PD, compared to HD, was significantly higher (58% vs. 44%), and a nonsignificant trend occurred of more people receiving PD having surgical intervention for hernias (7% vs. 4%) in 1 study.[361]

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 of those who choose one dialysis modality versus the other, or those who have different types of CKD.

For the comparison of dialysis modalities among people with ADPKD (Supplementary Table S13[358–361]), the only outcome critical for decision-making that was reported by more than 1 study was all-cause mortality. The outcome had a low grade of certainty of evidence because the studies had some methodological limitations (related to the method for adjustment for confounders or lack of adjustment) and, even

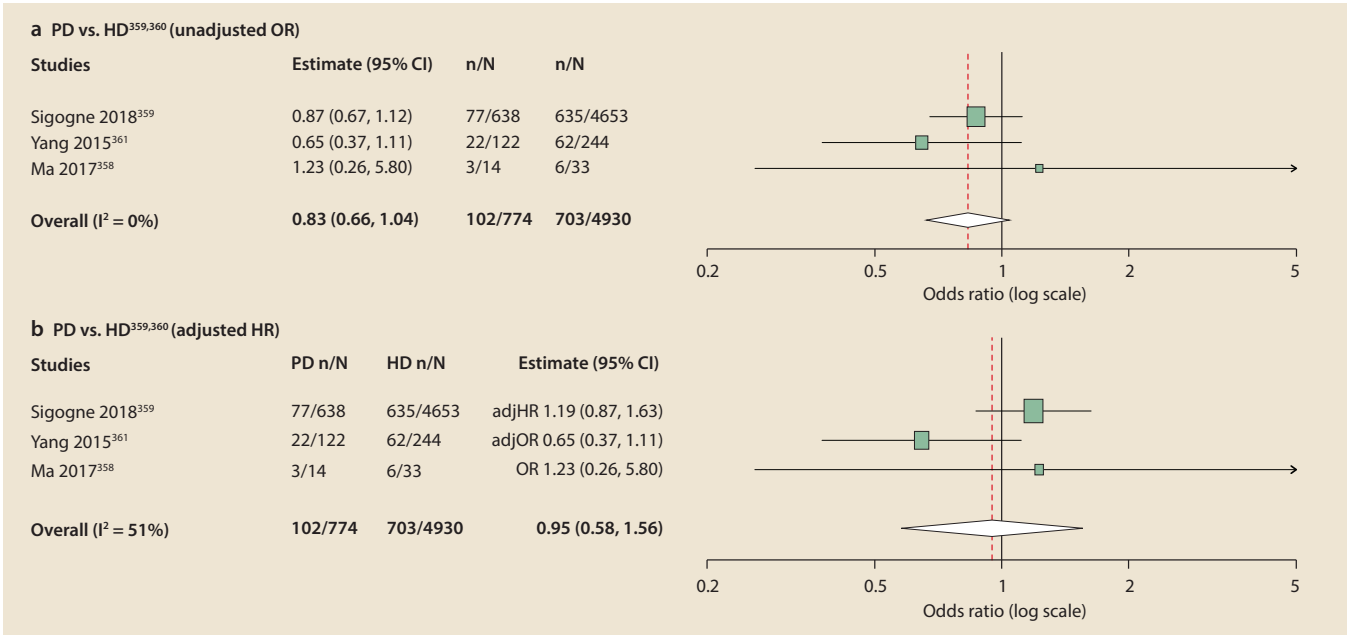


Figure 23 | (a) Unadjusted and (b) adjusted all-cause death with peritoneal dialysis (PD) versus hemodialysis (HD) in autosomal dominant polycystic kidney disease. adj, adjusted; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

in aggregate, a somewhat imprecise effect estimate. The other critical outcome of peritonitis was reported by a single study with no methodological limitations, thereby also providing a low grade of certainty of evidence (the highest possible grade of certainty for a finding that has not been replicated). The studies reporting on the important outcome of tolerability mostly reported on only switching from PD to HD (not vice versa), meaning that the studies had methodological limitations, indirectness of the outcomes, and incomplete reporting. However, a large, implied lower tolerability occurred among those on PD, compared to those on HD. Thus, overall, for tolerability, the grade of certainty of evidence was low. A single small study reported on the important outcome of risk of hernias, providing a very low grade of certainty of evidence. Studies did not report outcomes for numerous critical and important outcomes. Overall, based primarily on the low grade of certainty of evidence for the critical outcomes of mortality and peritonitis, we concluded that the grade of certainty of evidence is low for the direct comparison of PD versus HD in people with ADPKD.

For the comparison of people with ADPKD or other types of CKD who are receiving PD (Supplementary Table S14[358,359,362–371]), we found a moderate grade of certainty of evidence for both the outcome critical for decision-making—peritonitis—and the important outcome of 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 to lack of adjustment) but yielded consistent, direct, and precise summary estimates. The studies reporting on the critical outcome of all-cause mortality had inconsistent findings; thus, the grade of certainty of evidence was low 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 a very low grade of certainty of evidence. The 2 other important outcomes with data—dialysis efficiency and abdominal wall hernia—had serious methodological limitations and therefore were deemed to have a low grade of certainty of evidence. Studies did not report outcomes for numerous critical and important outcomes. Overall, given the low grade of certainty of evidence for all-cause mortality, and the lack of evidence for most other critical outcomes, we concluded that the grade of certainty of evidence is low, for the comparison of PD in people with ADPKD versus in other people.

Values and preferences. The choice of PD versus HD is an important decision for a person with kidney failure due to ADPKD. Clinical consideration has been given to the possibility that PD may be disadvantageous in the context of ADPKD, due to the risk of peritonitis caused by diverticular disease, reduced dialysis adequacy, and the risk of hernias related to kidney size, increased abdominal pressure, and reduction in abdominal volume.[360,361] This possibility must be balanced against patient preference and certain advantages of PD related to autonomy, QoL, and preservation of residual kidney function. Although the incidence of hospitalization for infection and possibly of surgical intervention for hernia in people receiving PD was increased, no apparent increase in mortality occurred.

Resource use and costs. The availability of HD in settings with low levels of resources may be limited, and PD offers greater access to KRT. PD is generally cheaper than HD and offers greater access to KRT in countries or localities that have resource constraints, or where HD slots are limited. Home HD may be considered as it is less expensive. PD does not require the same levels of expertise and hardware that are required to run an HD unit, a difference that may be important in settings with low levels of resources.

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

Rationale

Given the low grade of certainty of evidence, comparing the potential benefits of one dialysis modality versus another in people with ADPKD was difficult. Also with a low grade of 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, in conjunction with their dialysis provider, whether the future risk of developing specific complications (e.g., abdominal hernia, peritonitis) with the use of PD is acceptable.[357]

Research recommendations

- Better quality studies are required to address outcomes comparing PD versus HD in people with ADPKD, such as those on 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, and 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 versus 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 after the third and fourth decades of life (Figure 24). Thus, the primary goal of medical treatment in ADPKD is to delay the onset of kidney failure.

As outlined in Chapter 7, lifestyle interventions (including smoking cessation, having a BMI <25 kg/m^2, dietary sodium restriction, intake of <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,[237] due to disease-specific effects on reducing kidney cyst growth.[140,141,372,373]

Inhibition of arginine vasopressin (AVP). Pharmacologic interventions targeting the action of the antidiuretic hormone AVP are presently the cornerstone of treatment in people with ADPKD who are at risk of rapid disease progression. Preclinical data, obtained both *in vitro* and *in vivo*, have identified that AVP has a pathologic role in ADPKD, of promoting kidney cyst growth during the postnatal period.[374,375] From a therapeutic viewpoint, the effects of circulating AVP on kidney cyst growth

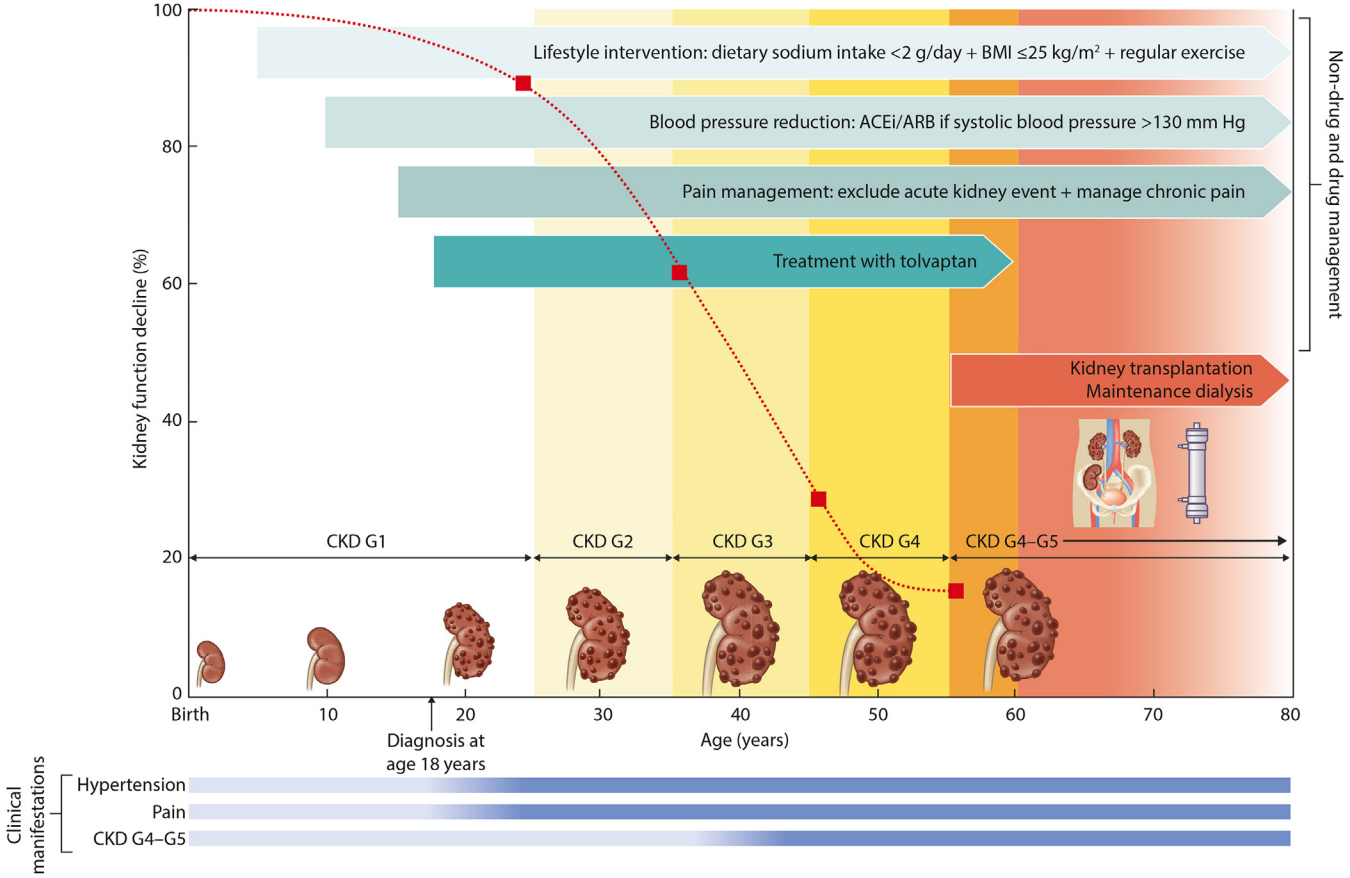


Figure 24 | Schematic diagram depicting the life journey and therapeutic considerations of a hypothetical person with rapidly progressive autosomal dominant polycystic kidney disease. At birth and during early childhood, the kidneys may be macroscopically normal, and the diagnosis typically is made by a screening ultrasound performed at or after a patient age of 18 years. With age, the frequency of clinical manifestations increases, as depicted by the change in the color gradient of the blue bars: Hypertension is most commonly detected from about age 25 years, as shown by the blue gradient 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 G1 and G3) slows the progression of kidney function decline. The dotted line depicts the fall in the glomerular filtration rate. The duration of disease at each CKD severity level (between G2–G5 and before dialysis or kidney transplantation) is about 2–10 years, 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.

Table 8 | Approaches to reduce AVP activity in ADPKD

Factors	Increased water intake	V_2 receptor antagonist (tolvaptan)
Mechanism	Suppression of AVP release by lowering plasma osmolality	Selective blockade of AVP binding on V_2 receptors
Administration	Drinking water during waking hours	Split-dose tablet (1 tablet upon waking, and 1 tablet 8 h later)
Effect on water intake	Voluntary increase (≥2 l/d)	Involuntary increase due to thirst and aquaresis (>3–7 l/d)
Effect on circulating level of AVP	Reduced level	Increased level
Indication for use in ADPKD	All people with eGFR >30 ml/min per 1.73 m^2	Selected high-risk groups due to cost and side effects
Efficacy to ↓ urine osmolality to 300 mOsmol/kg	∼50% of participants in 3-yr (PREVENT-ADPKD trial)[257]	∼70% of ADPKD participants, >3 yr treatment in the TEMPO 3:4 trial
Efficacy to ↓ TKV in ADPKD	No (PREVENT-ADPKD trial)[257]	Yes (TEMPO 3:4)
Efficacy to ↓ long-term eGFR decline	No	Yes (∼1 ml/min per 1.73 m^2) (TEMPO 3:4 and REPRISE trials)[28,29]
	No data on risk reduction for CKD G5 (PREVENT-ADPKD trial)[257]	No data on risk reduction for CKD G5
Adherence to treatment	∼50% over 3 yr (PREVENT-ADPKD trial)[257]	Real-world adherence declines over time and ∼75% after 3 yr[377,378]
Disadvantages	Long-term adherence is poor; pollakiuria, polyuria	Thirst/dehydration
	Reversible mild hyponatremia	Pollakiuria, nocturia, polyuria with potential impact on day-to-day living (occupation, habits)
	Environmental issues (bottled water)	Blood tests (every 1–3 mo)
		Hypernatremia; hyperuricemia
		Risk of hepatotoxicity
		Accessibility
Advantages	Access and low cost (tap water)	Standard dose
	More physiological suppression of AVP than V_2 receptor antagonist	Better 24-h inhibition

ADPKD, autosomal dominant polycystic kidney disease; AVP, arginine vasopressin; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PREVENT-ADPKD, Prevent Kidney Failure Due to Autosomal Dominant Polycystic Kidney Disease; REPRISE, Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD; TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume; V_2, vasopressin-2.

in ADPKD can be modified by at least the following 2 approaches, which are not mutually exclusive: (i) pharmacologic blockade of vasopressin-2 (V_2) receptors using tolvaptan (note that other V_2 receptor antagonists are available, but only the efficacy of tolvaptan has been evaluated in ADPKD); and/or (ii) increased water intake (Table 8).[258,376]

4.1 Tolvaptan

4.1.1 Indications for tolvaptan in ADPKD

Recommendation 4.1.1.1: We recommend initiating tolvaptan treatment in adults with ADPKD with an estimated glomerular filtration rate (eGFR) ≥25 ml/min per 1.73 m^2 who are at risk for rapidly progressive disease (Figure 25) (*1B*).

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 m^2. Additional benefits were a reduction in the incidences of kidney pain, and decreased rates of UTI, kidney stones, and hematuria. Shared and individualized decision-making should be undertaken when determining whether to initiate tolvaptan in all people with ADPKD, including those aged >55 years.

Key information

Balance of benefits and harms. Tolvaptan is an oral nonpeptide vasopressin receptor antagonist that specifically inhibits binding of AVP at the V_2 receptor of the collecting duct, causing the selective diuresis of electrolyte-free water (also known as aquaresis).[383]

Our systematic review found 3 RCTs, and 2 extension studies—a pooled, matched comparison of long-term tolvaptan-treated and untreated groups;[84] and a postmarketing analysis of harms.[28,29,385–389] 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, it was −2.7%; (95% CI: –3.3 to –2.1), both of which favor use of tolvaptan. UTIs were less common with use of tolvaptan (OR 0.65; 95% CI: 0.50–0.86), and the incidence of kidney stones and hematuria were reduced in the TEMPO 3:4 trial, associated with a decrease in first kidney-pain events (HR, 0.64; 95% CI: 0.48–0.86).[231] In one study,[28] the HR for risk of worsening kidney function was 0.39; 95% CI: 0.26–0.57, and the HR for kidney-pain reduction was 0.64 (95% CI: 0.47–0.89). An analysis of the

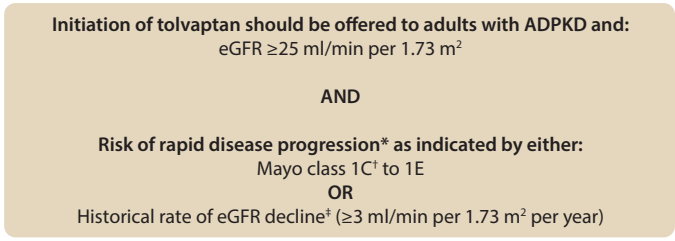


Figure 25 | The Kidney Disease: Improving Global Outcomes algorithm to decide in whom to prescribe tolvaptan. *Rapid disease progression is defined as having reached or being expected to reach kidney failure due to autosomal dominant polycystic kidney disease (ADPKD) before age ~60 years, the average age at which untreated people with ADPKD reach kidney failure. The use of age ~60 years is based on multiple cohort studies (not stratified by genotype) (European Renal Association–European Dialysis and Transplant Association [ERA-EDTA], mean age 58 years[379]; Genkyst cohort, 61.7 years[36]; Mayo PKD Database, 62 years[380]; Korea national cohort, 62 years[379]; and Australia and New Zealand Dialysis and Transplant Registry (ANZDATA registry), 60 years.[381] †Because some people with MIC subclass 1C may not have rapid disease progression, clinical judgment and evaluation should be made on a case-by-case basis and additional information could be used, particularly in the people with age-adjusted height-adjusted total kidney volume (htTKV) on the borderline of Mayo Image Classification 1B, to assess the risk for rapid disease progression (e.g., evidence of estimated glomerular filtration rate [eGFR] decline or of a reduced age-calibrated eGFR,[382] Predicting Renal Outcome in Polycystic Kidney Disease [PROPKD] score >6, family history with onset of kidney replacement therapy [KRT] at <60 years in ≥2 first-line family members, or novel biomarkers).[202] ‡If estimated glomerular filtration rate (eGFR) loss has likely alternative explanations (e.g., vascular disease, uncontrolled hypertension, diabetic nephropathy, proteinuria ≥1 g/d) and/or acute kidney injury, then initiation of tolvaptan use should be re-evaluated, even in the presence of rapid eGFR decline. In these cases, additional information (including magnetic resonance imaging or computed tomography imaging should be undertaken, if not previously performed; PROPKD score >6, a family history with onset of KRT at age <60 years in ≥2 first-line family members) should be acquired to ensure ADPKD as the primary reason for eGFR loss.

U.S. postmarketing 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.[386] 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 group than in the placebo group (5.6% vs. 1.2%; HR: 4.91; 95% CI: 2.29–10.53).[29] Other outcomes had imprecise estimates of effect or were not reported.

Notably, the evidence base is driven mainly by 2 multinational, pivotal RCTs (TEMPO 3:4 and REPRISE; Figure 26).[28,29]

In the TEMPO 3:4 trial, participants were aged between 18 and 50 years, with TKV ≥750 ml, and an estimated creatinine clearance rate of ≥60 ml/min, as determined by the Cockcroft-Gault formula.[28,29] In the REPRISE trial, age-dependent criteria for eGFR were used to categorize people who were at high risk (aged 18–55 years, and eGFR of 25–65 ml/min per 1.73 m^2; aged 56–65 years and eGFR of 25–44 ml/min per 1.73 m^2 with prior decline in eGFR >2 ml/min per 1.73 m^2 per year).[28,29]

The results of both trials demonstrated that tolvaptan treatment 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

TEMPO 3:4	CKD G1–G3a
Study population n=1445 18 to 50 years old TKV >750 ml in CKD	
Dose of tolvaptan* 120 mg/d (55%), 90 mg/d (21%), 60 mg/d (24%)	
Main results • Primary endpoint: reduced rate of increase in TKV: 2.8%/year in tolvaptan group vs. 5.5%/year in placebo • Secondary endpoints: slower decline in kidney function (reciprocal of the serum creatinine level, −2.61 [mg/ml]$^{-1}$/year vs. −3.81 [mg/ml]$^{-1}$/year, P <0.001); lower rates of worsening kidney function (2 vs. 5 events per 100 person-years, P <0. 001) and kidney pain (5 vs. 7 events per 100 person-years of follow-up; P=0.007).	
Adverse effects Tolvaptan associated with aquaresis and abnormal liver function tests and higher discontinuation rate (23% vs. 14% in the placebo group).	

REPRISE	CKD G3–G4
Study population n=1390 18–55 years old + (eGFR 25–65 ml/min per 1.73 m²) 56–65 years old + (eGFR 25–44 ml/min per 1.73 m²) Ability to tolerate tolvaptan after an 8-week run-in	
Dose of tolvaptan* 120 mg/d (61%), 90 mg/d (30%), 60 mg/d (10%)	
Main results • Primary endpoint: Reduced rate of decline in eGFR by −2.34 ml/min per 1.73 m² in the tolvaptan vs. −3.61 ml/min per 1.73 m² in the placebo; P <0.001).	
Adverse effects Reversible increases in the ALT to >3 times the normal range (5.6% in the tolvaptan group vs. 1.2% in the placebo group)	

Figure 26 | Summary of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO 3:4) and Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trials.[28,29] ALT, alanine aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TKV, total kidney volume. *Note that tolvaptan dose was split as 90/30, 60/30, or 45/15 mg/d.

endpoints (rate of increase in TKV and rate of decline in eGFR, respectively).[28,29] However, as the goal of medical treatment is to delay the onset of kidney failure, changes in eGFR have greater clinical relevance. In TEMPO 3:4, tolvaptan use reduced the eGFR loss by 36% per year (~1 ml/min per 1.73 m^2 per year) in early-stage ADPKD (aged 18–50 years, with CKD G1–G3).[28,29] The results of the REPRISE study extended these findings to later-stage ADPKD (defined by CKD G3–G4), for which tolvaptan use reduced the rate of decline in eGFR by approximately 1.27 ml/min per 1.73 m^2, compared to placebo.[28,29] Subgroup analysis of the REPRISE trial showed that people aged 18–55 years benefited, whereas those aged >55 years (n = 190) received no benefit. With only sparse evidence available from people aged >55 years, a conclusion about the use of tolvaptan in older adults is less clear. *Post hoc* analyses also revealed a reduction in pain events in the tolvaptan arm, in part due to a decrease in UTIs, kidney stones, and hematuria.[390]

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 occurring thereafter. This result might be due to the different mechanisms that explain the acute and chronic effects on reducing cyst-fluid secretion and cystic epithelial proliferation, respectively.[388]

The presence of risk of rapidly progressing ADPKD has been stated by regulatory agencies as a criterion for eligibility for tolvaptan treatment. However, the definition of risk of rapidly progressing ADPKD largely has been left to be determined by clinical consensus in different geographic areas, and global consensus is lacking. When imaging is available, the MIC, based on MRI or CT scanning, should be used as the primary imaging method for risk prediction and consideration of tolvaptan in routine clinical care (see Practice Point 4.1.1.2). An historical decline in eGFR also is used to determine the presence of risk of rapidly progressing ADPKD in the absence of advanced imaging. A confirmed annual eGFR decline ≥3 ml/min per 1.73 m^2, determined by multiple measurements of eGFR over 3–5 years, also may be utilized. Therefore, defining rapid progression in people with ADPKD, by either an historical decline in eGFR or the MIC, is important for assessing benefit from tolvaptan treatment.

The slope of eGFR should be evaluated with sufficient measurements of serum creatinine (SCr level; using isotope dilution mass spectrometry [IDMS] traceable assays),[237] to allow a reliable assessment of rate of decline and to avoid variations due to random day-to-day fluctuations in SCr level and therefore, eGFR.[204] The MIC is a practical tool for identifying people at risk for rapid progression. A *post hoc* analysis of the TEMPO 3:4 trial showed that equal benefit from tolvaptan use, on kidney growth and eGFR decline, was received in people with class 1C, 1D, and 1E.[391] Furthermore, measurement error may account for misclassification of people at the boundary of class 1B and 1C. Therefore, for people at the boundary of classes 1B and 1C, clinical judgment is required to determine their eligibility for tolvaptan therapy. For CKD in general, KDIGO has defined rapidly progressive decline in kidney function as that which is ≥5 ml/min per year. However, in people with ADPKD, a decline of eGFR of < 5 ml/min per year may be associated with kidney failure before age 58 years.[392] In the placebo arms of the REPRISE and TEMPO 3:4 studies, which were enriched with people who had rapid progression, the average annual rate of decline was approximately 3.5 ml/min per 1.73 m^2. In unselected cohorts of people with ADPKD, the average rate of decline was approximately 3.0 ml/min per 1.73 m^2, suggesting that a historical annual decline of ≥3 ml/min per 1.73 m^2 would be a good definition for rapidly progressive decline in kidney function.

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.[393] The aquaretic adverse events occurred within a median of 2 days of commencing tolvaptan use, and they were ranked by participant self-report as being most intolerable during the initial 3 weeks of treatment.[393] The main aquaretic side effects (tolvaptan use vs. placebo) were as follows: thirst (55.3% vs. 20.5%), polyuria (38.3% vs. 17.2%), and nocturia (23.2% vs. 5.4%).[393] At the maximal dose (120 mg/d), the mean urine volume increased by 3–7 l/d in people with CKD G1–G2. In people with CKD G4, the urine volume increase was slightly less, at 5 l/d.[393] In both pivotal trials, less than two-thirds (55%–61%) of people tolerated the highest dose of tolvaptan (120 mg/d, taken as 90 mg in the morning + 30 mg in the afternoon).[28,29] 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.[394,395] Younger people with ADPKD in earlier stages of disease progression are more sensitive to aquaretic symptoms, and this should be taken into consideration when uptitrating the dose.[393]

In the TEMPO 3:4 trial, after 3 years of therapy, 75% of subjects using tolvaptan indicated that they could tolerate their current dose for the rest of their lives, compared to 85% of subjects on placebo. These findings were corroborated by results in the open-label extension trial TEMPO 4:4.[38]

Typically, the liver transaminase elevations were mild and reversible when tolvaptan use was stopped, but 0.06% of people developed more serious liver injury. Tolvaptan use also causes a decline in eGFR during the first month of therapy (due to a combination of suppression of glomerular hyperfiltration and/or reduced kidney plasma flow, secondary to volume depletion), which stabilizes.[396] Additional side effects include hyperuricemia (3.9% vs. 1.9%), and rarely, gout (2.9% vs. 1.4%), compared to use of placebo, in the TEMPO 3:4 trial.[397] 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.[398] Recently, elevation of serum creatine kinase level has been reported in 28% of 97 people treated with tolvaptan.[399]

The main uncertainty regarding tolvaptan treatment is its long-term effect on reducing kidney failure (Figure 27). However, the effect of tolvaptan treatment on the rate of eGFR decline is accepted by regulatory authorities as a reliable

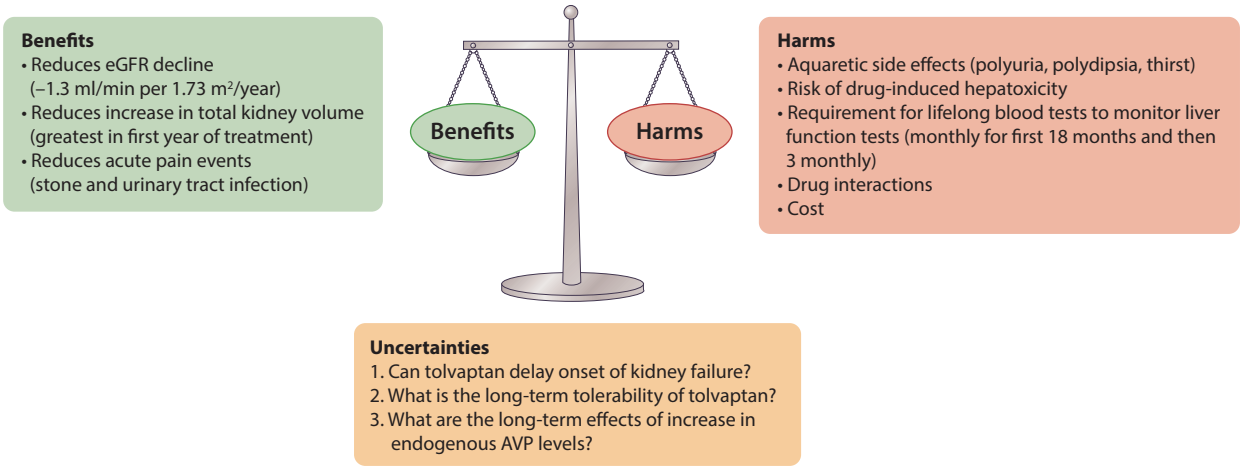


Figure 27 | Schematic diagram summarizing the harms, benefits, and uncertainties regarding long-term treatment with tolvaptan in people with rapidly progressing autosomal dominant polycystic kidney disease. AVP, arginine vasopressin; eGFR, estimated glomerular filtration rate. Adapted with permission from Chebib *et al.*[402]

surrogate for delaying the onset of kidney failure. The effect of tolvaptan treatment on the rate of decline in eGFR (1.3 ml/min per 1.73 m^2) is comparable to that with other kidney-protective agents used for other causes of CKD, such as ACEi,[400] but it could be less than that of others, such as SGLT2i.[401] Treatment with tolvaptan needs to be sustained for many years to prevent or delay kidney failure. Real-world adherence declines over time, with about 75% of people continuing treatment after 1–3 years.[377,378]

Certainty of evidence. The overall certainty of evidence was graded as moderate based primarily on the evidence for eGFR, with findings of a consistently low grade of certainty for other outcomes (Supplementary Table S15[28,29,384–386,389,398,403]). 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, some methodological concerns were present, reducing the grade of certainty of evidence. The critical outcome of change in kidney function had a moderate grade of certainty of evidence; however, no evidence was reported about kidney failure. Other critical outcomes (TKV, pain, and liver injury) had a low grade of certainty of evidence, due to only limited data being available for meta-analysis. Either no evidence or evidence with a very low grade of certainty was given for other critical outcomes, due to imprecision in effect estimates. The grade of certainty of evidence was moderate for the important outcomes, such as UTI, due to some methodological limitations, and serious polyuria, due to some methodological limitations and some inconsistency but large effect sizes. The grade of certainty of evidence was low or very low for other important outcomes (serious thirst, discontinuations due to adverse events), due to imprecision and inconsistency across studies. Based primarily on the moderate grade of certainty of evidence for eGFR, with supporting grades of moderate and low of certainty of evidence for other critical and important outcomes, we concluded that the overall grade of certainty of evidence is moderate.

Values and preferences. An unmet clinical need exists for a treatment to prevent or slow progression of disease and reduce the risk of kidney failure due to ADPKD. No other pharmacologic agents have been proven 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 drug-induced liver injury (Figure 27). These safety concerns require careful patient selection, meticulous compliance with maintaining hydration, and vigilant long-term clinical and laboratory monitoring. Thus, tolvaptan use is not suitable for all people with ADPKD, and patient selection for treatment should be based on criteria that indicate they have rapidly progressive kidney disease (MIC subclass 1C–1E, or an historical decline in eGFR, as shown in Figure 25), an absence of contraindications, and are tolerant of and adherent to monitoring. A reasonable expectation is that many people will choose to refuse tolvaptan treatment. Nevertheless, the advantages of tolvaptan use in slowing disease progression outweigh the disadvantages in people who are aged <55 years and meet the criteria of rapid progression, as specified in Figure 25.

Resource use and costs. Tolvaptan has regulatory approval for use with government subsidies in many, but not all, countries.[404] Historically the cost of tolvaptan has been very high.[405] However, in recent years, the cost has been reduced considerably, and generics have entered the market in several countries around the world. Although regional differences are present in price and reimbursement regulations, tolvaptan has generally become more affordable for people with ADPKD.

Tolvaptan use can be maintained lifelong, until a point in time close to when KRT is required. Although tolvaptan can slow progression, it may cause a heavy financial burden on people with ADPKD and their families, if no government or insurance subsidies are available. Tolvaptan treatment may also interfere with people's work or school because of their increased urination and thirst, and requires monthly visits for testing for the first 18 months, and then every 3 months

thereafter. In addition, some people may find that their work environment and their occupation are not suited to the use of tolvaptan.

Considerations for implementation. In most countries, tolvaptan has regulatory approval for use, and further real-world population cohorts and registry data will be beneficial for making future refinements in practice. Similarly, the treatment response in people with non-European backgrounds is not clear (88% of participants in the TEMPO 3:4 and REPRISE trials were reported to be White) and should be investigated further (see Research Recommendations).[28,29] Subgroup analysis (which could be underpowered) of this subpopulation in the REPRISE trial suggested that benefits are less certain (mean eGFR in non-White groups for tolvaptan vs. placebo use: –3.29 vs. –3.54 ml/min per 1.73 m^2; $P = 0.79$).[29] The long-term tolerability in young people, and tools that promote adherence, also require further investigation.

The suggestion has been made that tolvaptan use not be initiated when eGFR <25 ml/min per 1.73 m^2, as this has not been tested in RCTs and the benefits are likely to be limited. In people with such low GFR, the acute drop in GFR that occurs when tolvaptan use is initiated may offset any beneficial effects on the slope of eGFR loss. Furthermore, this reversible hemodynamic effect of tolvaptan use also suggests that tolvaptan use should be stopped in people with eGFR <15 ml/min per 1.73 m^2, as the small, predicted increase in eGFR may provide benefit in delaying the onset of KRT.[204] See Practice Point 4.1.1.1 regarding treatment of people aged >55 years.

Rationale

The Work Group concluded that most people who have 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 use in people with ADPKD with ≥1 year of follow-up. Although only 5 studies were identified, the grade of certainty of evidence was high that progression of kidney disease was slowed by 1.3 ml/min per 1.73 m^2 per year (33% relative reduction), compared to that with placebo use. This benefit was greatest in people aged ≤55 years who had eGFR ≥25 ml/min per 1.73 m^2, and either had established rapid progression or were at high risk for rapid progression. The pivotal studies reported that a reduction also occurred in kidney pain, and frequency of UTIs. The main risk for harm was a low risk of serious drug-induced liver injury (0.06% of participants; 5% risk of a liver enzyme increase), and this risk can be reduced by surveillance monitoring of liver function tests monthly for the first 18 months, and then every 3 months lifelong, 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 they are potentially adaptable and are reversible, upon 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, the long-term tolerability of and adherence to treatment are not clear.

Furthermore, the beneficial impacts of tolvaptan use on the long-term outcome event of developing kidney failure have been hypothesized but have not been validated in observational cohort studies. Given that tolvaptan is the first disease-modifying drug to slow progression in people at high risk for rapidly progressive disease, the Work Group concluded that, on balance, the benefits outweigh the harms and uncertainties.

The pivotal studies included adults with a diagnosis of ADPKD, based on imaging criteria, as defined by the Pei-Ravine criteria (if a positive family history is present) or >10 cysts per kidney on imaging in the absence of a family history (Figures 3–5).[28,29] 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 age-acquired kidney cysts)—and if required, molecular genetic testing (for cases in which imaging is equivocal; see Chapter 1). 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 use in the pivotal studies.

One trial has evaluated the safety and efficacy of tolvaptan use for 12 months in children and adolescents with ADPKD, with insufficient power to detect significant changes in htTKV. Tolvaptan exhibited pharmacodynamic activity when used in cases of pediatric ADPKD. Aquaretic effects were manageable, with few discontinuations.[387] To date, no trials have examined the efficacy of tolvaptan use in cystic kidney diseases other than ADPKD (i.e., ARPKD, tuberous sclerosis, HNF1B 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 determining whether to initiate tolvaptan in people aged >55 years with rapid progression.

Subgroup analysis of the REPRISE study results for those in the group aged >55 years with an eGFR <45 ml/min per 1.73 m^2 showed a nonsignificant difference between tolvaptan and placebo use in the rate of decline in eGFR (–2.54 vs. –2.34 ml/min, respectively; $P = 0.65$), despite rapid progression of CKD, as evidenced by a decline in eGFR >2 ml/min per year.[29] With increasing age, other comorbidities (e.g., diabetes, hypertension) are likely to contribute to declines in eGFR that will not be responsive to tolvaptan treatment. In a prospective observational cohort analysis of the ERA-European Dialysis and Transplant Association (EDTA), 20,483 people with ADPKD in 12 European countries (in the years 1991–2010) commenced KRT at ages between 57 and 58 years; most rapid progressors would have reached kidney failure by age 55 years.[392] Therefore, the remaining people not on dialysis will likely have slowly progressive disease, and

thus, they will not match the indication to be given tolvaptan prescription. The subgroup analysis of the REPRISE study was also limited by the small numbers ($n = 190$ people), making definitive decisions in specific people less clear. A *post hoc* observational analysis of the REPRISE trial in people aged >55 years with CKD G3 or G4 showed that the annual rate of eGFR decline was reduced, when this group was matched to a separate ADPKD cohort (Observational Study in Patients With Autosomal Dominant Polycystic Kidney Disease [OVERTURE]).[406]

Overall, given the lower quality of the evidence and the limited amount of data currently available for older adults, shared, individualized decision-making should be undertaken to balance the risks and possible benefits in people aged >55 years who have proven rapidly progressive disease.

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

The historical rate of eGFR decline is a widely used marker to define risk for progression (Figure 25). However, the MIC is currently the best imaging tool available to define risk for progression of ADPKD, and it can be particularly helpful for clinical decision-making for initiation of tolvaptan use during early-stage ADPKD when eGFR is preserved.[32] Using MRI (or CT scan), cases are subdivided into those that are typical versus atypical ADPKD. In typical cases, TKV is measured by stereology (TKVs) or estimated by the ellipsoid equation (TKVe), using MRI, and subclassified according to age-adjusted growth rates for htTKV ranges, into subclasses 1A–1E. Thus, those in subclasses 1A and 1B have slower progression of disease, whereas those in classes 1C, 1D, and 1E have rapid progression. People in ADPKD subclasses 1C–1E should be considered for treatment with tolvaptan. Scans should be reviewed by experienced radiologists and nephrologists to ensure that correct classification occurs. Ideally, the assessment of MIC is determined using MRI, to avoid radiation exposure.

Since its development in 2015 by Irazabal *et al.*,[32] the MIC has been validated in a number of large cohort studies (e.g., the worldwide OVERTURE study[407] and the Korean KoreaN cohort study for Outcome in patients With Polycystic Kidney Disease [KNOW-PKD] cohort[183]).[408] The main limitations in using the MIC as a tool for decision-making for tolvaptan use is the accessibility to MRI (cost and reimbursement; contraindications to MRI) and TKV stereology, and the lack of long-term validation studies. The lack of accessibility to formal stereological measurements of the kidney can be overcome by using the ellipsoid formula, bearing in mind that MRI ellipsoid underestimates TKV (by a mean of –3.2%) and misclassifies into the high-risk Mayo subclasses (1C–1E) in ~11% (PPV 96%, NPV 90%), as compared to TKV stereology.[195] In addition, the inability to perform MRI for kidney volume measurement (due either to a lack of availability or to contraindication) may be overcome by using low-dose or ultra-low-dose CT[409–411] or ultrasound (TKV underestimation –11%; high-risk MIC misclassification 22%; PPV 98%; NPV 95%).[195]

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

The PROPKD score provides an additional framework that can be used to identify risk for progression, in cases in which historical rate of decline in eGFR and/or MIC are equivocal and do not meet criteria (as described in Figure 25). The PROPKD score was developed from a cross-sectional study of 1341 participants from the Genkyst cohort and used to evaluate the influence of clinical and genetic factors on kidney survival.[36] A scoring system with scores ranging from 0 to 9 points was developed, based on demographics and disease characteristics, as follows: male, 1 point; hypertension before age 35 years, 2 points; first urological event before age 35 years, 2 points; *PKD2* mutation, 0 points; nontruncating *PKD1* mutation, 2 points; and truncating *PKD1* mutation, 4 points.[36] Three risk categories were defined, as follows: low-risk (0–3 points); intermediate-risk (4–6 points); and high-risk (7–9 points) 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.[36]

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

Tolvaptan treatment is unlikely to impact the decline in kidney function that is due to other causes of CKD. Thus, ruling out other causes of rapid eGFR decline in people, before starting therapy, is important. Doing so is especially important in older people in whom comorbidities, such as diabetes, hypertension, and heart failure, may be present and may cause a decline in kidney function unrelated to ADPKD. Another clue is the presence of heavy proteinuria that may indicate another form of CKD in addition to ADPKD. The rate of loss of kidney function in people with ADPKD tends to be linear,[412] 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 use in ADPKD

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

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

Table 9 | Checklist of contraindications to initiating and/or maintaining tolvaptan use

Absolute
- Planning pregnancy, pregnancy, or breastfeeding
- Medical conditions associated with or at high risk of volume depletion
- Inability to respond to or perceive thirst
- Uncorrected baseline hypernatremia
- Urinary tract obstruction
- Strong CYP3A inhibitors[a]
- Significant liver disease unless due to PLD
Relative
- eGFR at initiation <25 ml/min per 1.73 m^2
- History of gout or hyperuricemia
- Moderate CYP3A inhibitors[b], P-gp inhibitors[c], grapefruit and Seville orange consumption
- Urinary incontinence

CYP3A, cytochrome P450, family 3, subfamily A; eGFR, estimated glomerular filtration rate; PLD, polycystic liver disease; P-gp, P-glycoprotein.
[a]For example: ketoconazole, itraconazole, clarithromycin, lopinavir, ritonavir, and indinavir.
[b]For example: amiodarone, erythromycin, fluconazole, diltiazem, verapamil, grapefruit and Seville orange, imatinib, and fosamprenavir—which can increase tolvaptan exposure, and reduction of dose may be necessary.
[c]For example: 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.

The relative and absolute contraindications for tolvaptan use are listed in Table 9.

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 (CKD G4–G5). No data are available regarding the use of tolvaptan in pregnancy, and the potential risk of teratogenicity.

Pregnant women or those planning pregnancy should discontinue use of tolvaptan. Tolvaptan use should be avoided in lactating women. As the major side effect of tolvaptan use is aquaresis, its use should be avoided if hypernatremia or hypovolemia is present, or if a predisposition to hypernatremia or hypovolemia is present. Because of the risk of severe liver injury occurring with tolvaptan use, it should be avoided in those with significant hepatocellular liver disease. The latter group does not include those with PLD, as liver cysts derive from the intrahepatic biliary epithelium and, thus, PLD is not considered a hepatocellular disease.

The incidences of both hyperuricemia and gout were increased in the tolvaptan arm, compared to the placebo arm, in the TEMPO 3:4 trial (3.9% vs. 1.9% and 2.9% vs. 1.4%, respectively) but this did not lead to drug discontinuation. Long-term follow-up data from the REPRISE trial showed that incidences of hyperuricemia and gout were 2.8% and 4.7%, respectively.[398] In a prospective cohort study of 163 participants receiving tolvaptan for 1 year, the level of serum uric acid rose within the first month after starting tolvaptan treatment, and it increased the use of urate-lowering drugs over a 1-year period.[413]

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) is contraindicated. The use with moderate CYP3A inhibitors (e.g., amiodarone, erythromycin, fluconazole, diltiazem, verapamil, grapefruit, imatinib, and fosamprenavir) can increase tolvaptan exposure, and a reduction of dose may be necessary, and grapefruit intake should be avoided. A similar caution is given in relation to P-glycoprotein inhibitors (e.g., calcium-channel blockers, cyclosporin, dabigatran etexilate, digoxin, erythromycin, loperamide, protease inhibitors, and tacrolimus).

Statins may be prescribed safely in ADPKD, with careful attention to liver function tests (LFTs). In a *post hoc* analysis of the pivotal tolvaptan trials, no difference occurred in the incidence of statin-related adverse events in the tolvaptan-plus-statin group, compared to the placebo-plus-statin group.[414]

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).

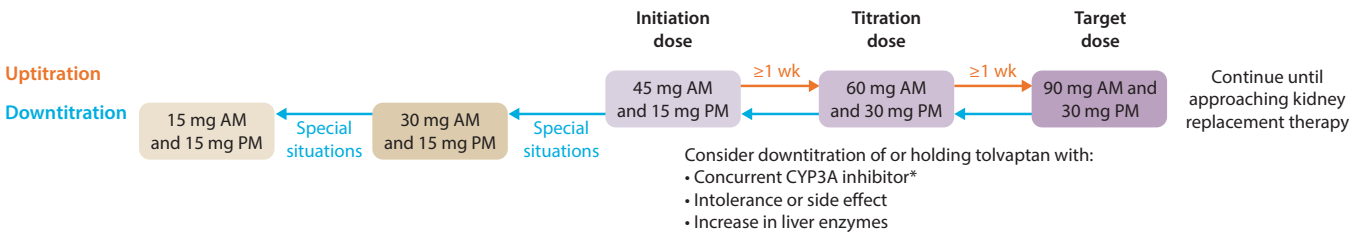


Figure 28 | Commencement of and titration approach to tolvaptan use in autosomal dominant polycystic kidney disease. *Examples of strong cytochrome P450, family 3, subfamily A (CYP3A) inhibitors (reduce clearance by >80%) are as follows: antifungals (itraconazole, ketoconazole); antibiotics (clarithromycin);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

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 use should be discontinued prior to pregnancy, during lactation, and prior to the commencement of KRT.

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

The practice points list the dosage regimens for tolvaptan that have been investigated, and those used in clinical trials of people with ADPKD that led to regulatory approval, as applicable. The asymmetric twice-daily dosage delivers the likely maximal aquaretic effects during the day, with the lower, midday dosage designed to mitigate the aquaretic effect during the night. Additionally, this is the minimum effective dose that has been investigated. People working night shifts should match the time they take their doses to the time of day they are awake. People unable to tolerate a 45 mg/15 mg dose can be downtitrated to 30 mg/15 mg or 15 mg/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 in whom these reduced doses are sufficient to maintain continuously hypotonic urine.

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 protocol in the clinical aim. The goal is to achieve maximal clinical effect and the desired clinical outcomes in a manner consistent with the outcomes observed in the tolvaptan clinical trials. Monitoring through uptitration includes kidney function, blood electrolyte (particularly sodium levels), and LFT monitoring in blood samples taken in the morning, before the dose of tolvaptan, for the most accurate assessment. Serum sodium levels may inform on the adequacy or excess of water intake, if hypernatremia or hyponatremia, respectively, develops. Future research should investigate the time-response to dosage uptitration and long-term efficacy assessment.

The goal of uptitration is to maximally achieve sustained inhibition of the V_2 receptor on kidney cyst growth and kidney function decline, while allowing behavioral adaptation to the aquaresis. A stepwise dose escalation is indicated, along with close engagement between the prescribing healthcare provider and the patient, for assessment of side effects and laboratory monitoring. Dose adjustment is not required in people with kidney function impairment. Tolvaptan therapy should continue at the highest-tolerated dose until KRT commences, unless an objective indication is present to pause, cease, or downtitrate sooner. Some uncertainty remains as to whether potential indications or individualized scenarios exist in which consideration should be given to tolvaptan use 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 the REPRISE trial and in its open-label extension trial in people with eGFR 15–29 ml/min per 1.73 m^2 suggested that tolvaptan use has a beneficial effect in this population.[389] Given the sparseness of related evidence and experience, shared decision-making is indicated to maximize benefit within a scope of acceptable tolerance and minimized clinical risk.

No specific biomarkers have sufficient specificity or sensitivity to verify the effectiveness of tolvaptan use on disease progression. As a direct marker of the action of V_2 signaling on the kidney tubule, urine osmolality has been considered as a potentially useful marker of ADPKD progression.[300,415] *Post hoc* analysis of the TEMPO 3:4 trial results 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.[416] Although urine osmolality from a spot urine test provides initial indirect verification of vasopressin blockade, serial measurement during tolvaptan therapy probably has limited clinical utility. In a *post hoc* analysis of the TEMPO 3:4 trial, ~81% of participants receiving tolvaptan achieved a urine osmolality <300 mOsm/kg, and no additional benefit occurred to disease progression when decreasing to <250 mOsmol/kg.[416] These data are limited, as a urine osmolality measure from a 24-hour urine test (which was not measured in the TEMPO 3:4 trial) is superior to a measure of osmolality from a spot urine test.[417] Moreover, a specific value for urine osmolality as measured from a spot test was not targeted as a goal in the pivotal trials.[28,29] Plasma copeptin, a surrogate marker of AVP, has been explored as a potential future biomarker of disease progression and tolvaptan treatment effect, although this possibility requires clinical validation before such usage can be applied routinely in clinical practice.[418]

No published data are available on the use of tolvaptan in pregnant women. Animal data show that tolvaptan crosses the placenta and causes embryo-fetal toxicity at high doses, and also is excreted in breastmilk.[419] Therefore, tolvaptan is a class-D category drug, and its use is contraindicated in pregnancy and during periods when breastfeeding is taking place, due to the potential risk for teratogenic effects. The impact, if any, of treatment interruptions on disease trajectory has not been adequately studied. Tolvaptan use should be ceased prior to pregnancy, with a washout period of a minimum of 4 weeks, as tolvaptan has a long-lasting metabolite (DM-4103, half-life >180 hour).[420]

4.1.4 Counseling people with ADPKD who are receiving tolvaptan

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

Practice Point 4.1.4.2: Education should be provided to people with ADPKD regarding the effect of tolvaptan to increase urinary water loss (such as thirst, polyuria, nocturia, and pollakiuria), the need to drink enough water to replace urinary losses, as well as strategies to minimize and manage anticipated aquaretic effects to ensure long-term tolerability.

As with any therapy, the relative benefits and harms should be discussed before initiating tolvaptan use. As noted above, the major benefit in people appropriate for such treatment is a reduction in the rate of kidney function decline (25%–33%), equating to a 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 LFT 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 and/or workplace and hobbies, should be actively considered and discussed.

At present, evidence is insufficient 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, suggesting that reducing the dietary solute load may mitigate tolvaptan-induced aquaresis.[421] Instead, focus should be placed on discussion around medication intake timing and administration to manage these potential side effects. The Work Group recognizes that long-term tolerance of tolvaptan is likely to be maximized by open and meaningful discussion and education between a treating healthcare provider and a patient.

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

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

People with ADPKD who are undergoing surgical procedures or who experience an acute medical event that predisposes them to intravascular volume depletion should interrupt tolvaptan treatment. An advisable approach may be for people with ADPKD, their kidney healthcare provider, and their primary care physician to consider a "sick-day" plan while they are being treated with tolvaptan. For instance, in cases of increased fluid losses (such as vomiting, diarrhea, fever due to acute infection), excessive sweating, and/or not being able to drink, temporary interruption of tolvaptan should be implemented until clinical advice or a remission of those circumstances indicates resumption is appropriate. Rapid acute complications may occur if people continue tolvaptan treatment while they are unable, either partially or fully, to replace urinary losses due to aquaresis. Tolvaptan treatment interruption also is indicated when clinical monitoring cannot be undertaken, especially monthly kidney and liver function monitoring within the first 18 months of tolvaptan treatment. In addition, in exceptional circumstances, a temporary short-term "drug holiday" may be required for convenience (e.g., on a long car journey or flight).

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.

Tolvaptan use is associated with an increased risk for idiosyncratic drug-induced liver injury. Approximately 5% of people with ADPKD treated with tolvaptan in clinical trials displayed an increase in transaminases that was more than 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 the alanine aminotransferase (ALT) level increases to >3-fold the ULN, at least once, in 4.4% of the tolvaptan group versus 1% of the placebo group.[28,388] Among 1271 people treated with tolvaptan, 3 met

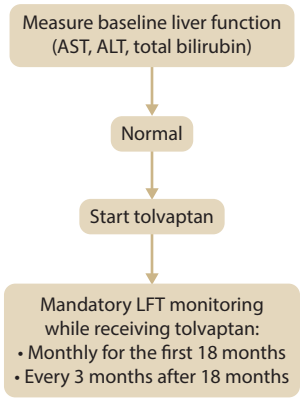


Figure 29 | Recommended monitoring for the early detection of drug-induced liver injury in people with autosomal dominant polycystic kidney disease on chronic treatment with tolvaptan. Note: In some countries, regulatory authorities recommend monitoring liver function tests (LFTs) at 2 and 4 weeks in the first month after starting tolvaptan use. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

the Hy's law criteria (i.e., a serum ALT level >3 times the ULN, and a bilirubin level >2 times the ULN), associated with a 10% risk of progression to acute and irreversible liver failure. The increases in ALT level occurred most often during the first 18 months of treatment and resolved within 1–4 months after tolvaptan treatment cessation.[420,422] Based on these data, in the REPRISE trial, LFTs were monitored on a monthly basis.[29] In this study, ALT level increases >3 times the ULN occurred in 5.6% of treated people, and 1.2% of people on placebo. However, likely due to this more frequent monitoring and consequent earlier discontinuation of tolvaptan use, no one met the Hy's law criteria in this study. A case of tolvaptan-associated liver failure requiring liver transplantation has been reported.[423] However, as noted above, an analysis of the U.S. postmarketing REMS database found that serious or potentially fatal liver events occurred in 0.06% of treated participants, with no deaths or liver transplants recorded.[386]

The mechanism of tolvaptan-induced liver injury is largely unknown, and is likely idiosyncratic.[422] This elevation in aspartate aminotransferase (AST)/ALT level is usually reversible upon discontinuation of tolvaptan use. A pooled analysis of safety data from prospective clinical trials consisting of 2900 people treated with tolvaptan showed that among 38 people rechallenged with tolvaptan use after the initial drug-induced liver injury episode, 30 displayed a return of increased liver enzyme levels.[420] This study identified a signature pattern of susceptibility to tolvaptan hepatotoxicity, which includes the following: (i) onset of hepatocellular injury, usually within 3–18 months of starting the drug and injury; and (ii) gradual resolution over 1–4 months following discontinuation of tolvaptan treatment. The absence of Hy's law cases in the REPRISE trial and the long-term extension trial corroborated the recommendation that liver enzyme monitoring be conducted during the first 18 months of tolvaptan treatment, and every 3 months thereafter, to detect and manage increases in liver enzyme levels.

Following regulatory approval by the U.S. FDA, all physicians prescribing tolvaptan for ADPKD in the U.S. must be trained and certified to appropriately apply the REMS program, and the European Medicines Agency (EMA) has implemented a risk management plan that includes education of both prescribing physicians and people with ADPKD. Based on the rare severe cases that fulfilled the Hy's law criteria, the risk management plan that was implemented requires close monitoring of levels of hepatic transaminases, total bilirubin, and alkaline phosphatase (Figure 29).[204] Therefore, mandatory to this approach is 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.[378,422,423] This practice point was based on the previously mentioned data that almost all cases of liver abnormalities triggered by tolvaptan use 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.[29]

The management of abnormal LFTs detected during tolvaptan treatment varies among countries and should follow local regulatory guidelines and product information. An algorithm suggested by a group of investigators who participated in the TEMPO 3:4 and REPRISE studies is shown in Figure 30.

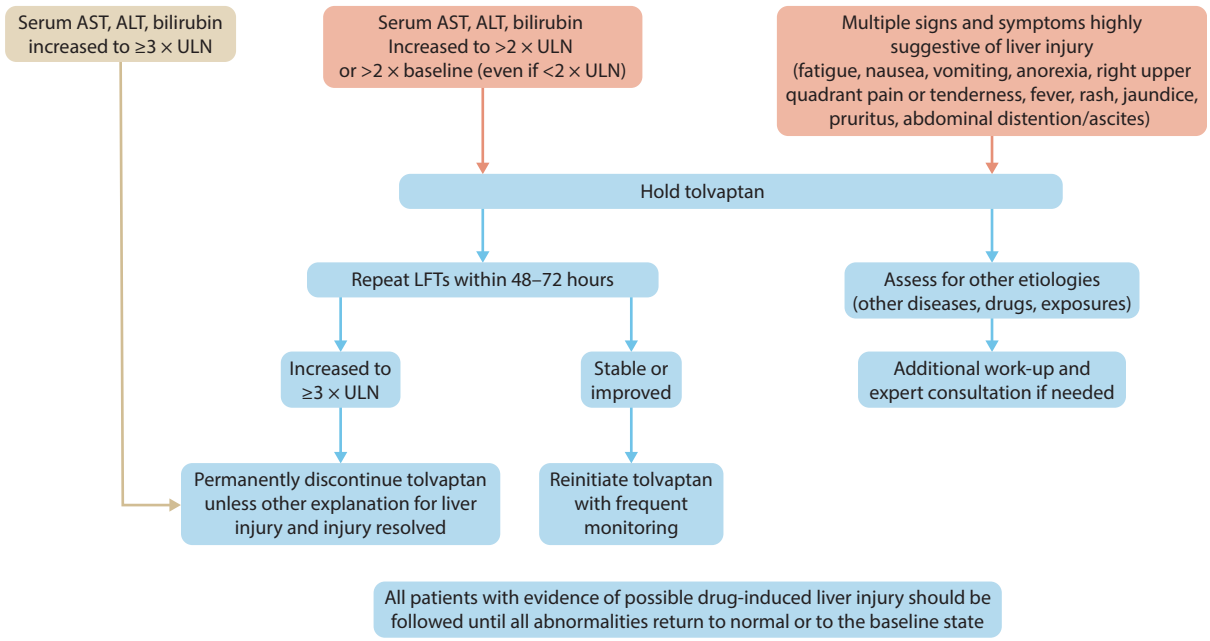


Figure 30 | Algorithm summarizing recommendations for evaluation and management of potential tolvaptan-induced liver injury. ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; ULN, upper limit of normal. Reproduced from Chebib *et al.*[402]

4.1.6 Management and risk mitigation of aquaretic side effects

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

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

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

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

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

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. A point that must be noted is that the increase in urine volume is expected to be higher in younger people with a higher GFR.[416,424] Initiating the treatment on a weekend, or on a nonworking day, is a good approach, to facilitate the adjustment to the aquaretic response. Indeed, the aquaretic effect becomes more tolerable in days to weeks following treatment initiation. People should be instructed to significantly increase the amount of fluid ingestion, to appropriately match urine output. The ideal source of fluid is water, whereas fluids with high sugar, sweetener, or fat contents should be avoided. Water intake, ideally, should occur prior to the onset of thirst, and definitely at the first sign of thirst. People should hydrate before bedtime, and again after each episode of micturition, in either the day or night.[402] People should be instructed to monitor their body weight regularly as a potential indicator of dehydration.

Although nocturia may limit tolerance, most people included in studies have tolerated this side effect of tolvaptan use.[393,425] Individual adjustments to the treatment may include adapting the schedule, timing, and doses of tolvaptan to people's activities. If nocturia remains a seriously bothersome effect that may result in nonadherence, reducing the second daily dose may be an alternative, despite a potential reduction in V_2 receptor blockade efficiency.

Healthy eating (as described in Practice Point 7.1.1.) may have a modest effect on reducing tolvaptan-induced polyuria.[204,402] Lowering dietary sodium intake, as part of healthy eating, may reduce urine output by decreasing the excreted load of osmotically active solutes.[376] As discussed in Chapter 7, minimizing salt intake also has a beneficial effect on kidney disease progression and facilitates BP control.[141,142] Moderate reduction in protein ingestion may also contribute to reduction of aquaresis.[376]

The use of tolvaptan causes nephrogenic diabetes insipidus, resulting in substantial polyuria.[426] The diuretic hydrochlorothiazide is an established therapy for nephrogenic diabetes insipidus, as it is able to decrease urine output by around 30%.[427] In addition, metformin has been shown to decrease urine output by almost 50% in tolvaptan-treated rats.[428] In this scenario, the suggestion has been made that either thiazide diuretics and/or metformin could be concomitant treatments to mitigate tolvaptan-induced aquaresis in people with ADPKD.[394] This hypothesis was supported by 2 small crossover trials of people treated with tolvaptan, in which short-term treatment with thiazide diuretics (trichloromethiazide, hydrochlorothiazide) or metformin reduced urine volume, as measured in a 24-hour urine test, by 21%–25%, and improved QoL.[394,395] However, the long-term effect of these interventions, which could potentially influence tolvaptan-induced kidney protection in people with ADPKD, is not known. A planned trial will evaluate this question (NCT05373264, comprising 300 participants). Currently, we advise against using a thiazide diuretic or other concomitant medication to mitigate tolvaptan-induced aquaresis.

As discussed in Recommendation 4.1.1 and Practice Point 4.1.3.4, treatment with tolvaptan can be maintained in people with eGFR <25 ml/min per 1.73 m^2, close to the commencement of KRT.[389] Furthermore, vasopressin has acute hemodynamic effects on glomerular filtration, and it activates tubuloglomerular feedback and afferent glomerular arteriole vasodilation (through renin release and efferent glomerular arteriole vasoconstriction).[28,29] Thus, the withdrawal or initiation of tolvaptan use may increase or decrease, respectively, eGFR by ~ 5%–10% in individual people.[429,430]

Published data on the clinical experience with use of tolvaptan in people with ADPKD who have undergone liver transplantation for PKD and who retain their native kidneys are extremely limited.[431] Thus, an individualized and multidisciplinary approach (involving the hepatology team) should be undertaken, taking into consideration eligibility (including or excluding other causes for eGFR decline, such as calcineurin nephrotoxicity) and risk–benefit analysis (tolvaptan-induced liver injury and drug–drug cytochrome 3A4 interactions between tolvaptan and tacrolimus).[431]

Research recommendations

- Observational cohort studies of tolvaptan in populations of non-European descent are needed.
- Studies are needed to evaluate the safety and efficacy of tolvaptan use in warm climates.
- Studies are needed to evaluate the time-response to tolvaptan titration.
- Long-term studies to evaluate the impact of tolvaptan use on development of kidney failure are needed.

- Studies are needed to compare the approaches of treating to maximally tolerated dose versus treating with a dose needed to maintain urine hypotonicity versus treating with 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 treatment.
- Studies are needed to assess biomarkers of progression of ADPKD.
- Studies to evaluate the ongoing postmarketing surveillance data and risk mitigation for tolvaptan-induced liver injury are needed.

4.2 Water intake in the absence of tolvaptan

4.2.1 General advice regarding water intake

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

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

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 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 m^2 who do not have contraindications (Table 10).[258,432–434] Maintaining adequate water intake and hydration status suppresses the pituitary release of AVP. As discussed, an early elevation of AVP level is an important driver of kidney cyst growth. Thus, in ADPKD, the goal of increasing water intake is to suppress the release of AVP to reduce kidney cyst growth.[258,434] As serum AVP is impractical to measure on a regular basis,[435] urine osmolality and volume are the prime indicators to assess the effectiveness of increased water intake. The basal circulating AVP level typically ranges between 0.5 and 2 pg/ml, which results in a urine osmolality that is ∼1–2-fold higher than the serum osmolality, and a urine volume of 1–3 l/d. 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 decreased. The maximal suppression of AVP to <0.5 pg/ml will produce a urine volume of >3 l/d, but it requires a level of fluid consumption that exceeds population-based recommendations (>8 l/d) and increases the risk for life-threatening hyponatremia.[436]

Table 10 | Relative contraindications for increasing water intake

• 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 that are used for BP control

BP, blood pressure; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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 to individualized, prescribed, and closely monitored water intake intended to reduce urine osmolality to ≤270 mOsmol/kg.[257] The mean 24-hour volume was 3 l/d in the intervention group, and 2.5 l/d in the control arm. The study found no significant differences between groups on the rate of htTKV, eGFR decline, systolic or diastolic BP, or pain.

In the judgment of the Work Group, minimal risks are associated with increased water intake to produce a urine output of between 2–3 l/d in people with an eGFR ≥30 ml/min per 1.73 m^2 and without contraindications to excreting a solute load (Table 10). In large studies, most people with ADPKD had a mean urine volume of 2.4 l/d at baseline.

Furthermore, in the El-Damanawi *et al.* study and the Prevent Kidney Failure Due to Autosomal Dominant Polycystic Kidney Disease [PREVENT-ADPKD] trial, in which people with eGFR ≥30 ml/min per 1.73 m^2 increased water intake, approximately 10% of people developed mild reversible hyponatremia without clinical significance.[257,437] In addition, adverse events and average withdrawals from the PREVENT-ADPKD study were similar between the increased-fluid-intake group and the usual-fluid-intake group.[257]

Maintaining increased water intake to reduce vasopressin over prolonged periods of time is likely to be difficult for most people. In the PREVENT-ADPKD study, the target osmolality of urine from a 24-hour test was achieved in only half of the people in the prescribed water group, whereas the target was achieved unexpectedly by 17% of the people in the *ad libitum* water group. Furthermore, serum copeptin levels were not different in the 2 groups. Possibly, additional strategies to remind people to drink increased volumes, even when they are not thirsty (such as a smart water bottle or other reminders), might enhance water intake.[438] Even then, achieving suppression of AVP with increased water intake, continuously over a 24-hour period, may be difficult. Results

of this study indicated that for both tolvaptan and placebo (recommended high level of water intake only), a greater decrease in urine osmolality at week 3 was associated with lesser TKV growth at month 12. Moreover, a potentially beneficial therapeutic response by people who regularly reach a urine osmolality of ≤270 mOsmol/kg only with water intake could not be excluded by the PREVENT-ADPKD study.

Qualitative research studies have revealed that people with ADPKD have a strong interest in water intake, and that they specifically requested information about how much to drink. Generic statements, such as "drink plenty of water," may be misunderstood by some people with ADPKD. Of particular concern, water intake that vastly exceeds population-based recommendations can lead to life-threatening hyponatremia.[436] 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.[436] In clinical trials, specific, individualized water prescriptions were developed, using the free water clearance formula. However, this approach 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 its cost effectiveness, compared to that of 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.[439] 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.[439] Although caffeine has been shown to stimulate cyst growth *in vitro*,[440] longitudinal data from 2 large cohort studies (the HALT and the Swiss ADPKD cohorts) showed that no differences occurred in kidney disease progression (TKV or eGFR) between coffee drinkers versus non–coffee drinkers.[128]

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).[376] 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, 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, due primarily to the sparseness of evidence, which came from only a single long-term trial (Supplementary Table S16[257]). 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 the sparseness of the evidence, we have concluded that the overall grade of certainty of evidence is very low.

Values and preferences. The Work Group placed a high value on the potential benefit of slowing progression and on the low risk for harm and the low value of 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; the intervention also offers wide availability, simplicity, low cost, and a good safety profile.

No evidence indicates that the source or type 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 increasing water intake as a therapy for ADPKD. Previous self-reported estimates indicate that most people (61%) with ADPKD probably have a high habitual intake of fluid (≥2 l/d), induced by their healthcare providers, based on previous influential publications regarding its potential benefits.[258,434] 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 the 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).[441] However, as most people with ADPKD in clinical trials at baseline were defined as "higher" water drinkers (i.e., having a high level of water consumption), the Work Group concluded that no evidence at present indicates that these additional resources are required.

Considerations for implementation. The implementation of the intervention from the PREVENT-ADPKD study was resource-intensive (dietitian, self-monitoring of urine specific gravity, text-messaging). Despite this resource level, the increase in urine volume in 3 RCTs was ∼0.8 l/d, a level that declined with the longer duration of the study.[257,376,442] Thus, implementation could entail simply providing people who have ADPKD with individualized education on the importance of maintaining hydration (noting its limitations as a therapy) and opting for plain drinking water, and on recognizing symptoms of dehydration (thirst, headache, dark-yellow urine, reduced urine frequency, dizziness).

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 also was based on priorities specified by people with ADPKD and was designed to minimize confusion among people with ADPKD and their healthcare providers, in addition to the benefits of wide accessibility and the low risk associated with increased water intake. The Work Group specified a level of urine output to define increased water intake, as a means to simplify inter- and intraindividual variability in daily fluid requirements based on insensible losses, due to differences in physical activity, climate, and clothing.

The Work Group considered that ADPKD is a chronic disease in which dehydration should be avoided. The recommendations for a fluid-intake target are consistent with the adequate-intake target advised for the general population to prevent consequences associated with dehydration (2.6 l/d for adult men and 2.1 l/d for adult women). Of note, only 22% of the general population reaches these targets.[443] Moreover, the recommendation is also consistent with the target specified by the American Urological Association Clinical Practice Guidelines for the Prevention of Kidney Stones.[443a]

4.2.2 Precautions regarding increasing water intake

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

Increased water intake should be advised for only those 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 care, considering current active medical problems, medical history, physical examination findings, and laboratory investigations, should be performed to identify risk for fluid retention or life-threatening hyponatremia (Table 11). Trials have excluded people with comorbidities or risk factors for fluid retention and hyponatremia, including regular use of pharmacologic agents that reduce the kidney capacity to excrete free water and thereby increase risk for fluid retention (hypertension, weight gain) and life-threatening hyponatremia. The long-term use of diuretics and NSAIDs commonly is associated with hyponatremia (risk frequency between 1 in 100 and 1 in 1000), whereas other drug classes (antidepressants, antipsychotics, antiepileptics, opioids) are rare (risk frequency ≤1 in 10,000[257]). The risks and benefits for people with ADPKD are unclear.

Table 11 | Factors to be considered before advising increased water intake

History
• *Comorbidities*: 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 2–3 l/d? Is it compatible with the person's work environment?
• *Diet*: Does the person consume an ultra-low-sodium and/or protein diet (<60 mEq/d or <0.6 g/kg ideal body weight/d)?
• *Medications*: Does the person 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 volume overload (e.g., edema)?
Investigations
• Does the person have eGFR<30 ml/min per 1.73 m^2?
• Does the person have baseline hyponatremia (<135 mmol/l)?

AVP, arginine vasopressin; eGFR, estimated glomerular filtration rate.

Clinical trials of increased water intake in people with ADPKD excluded those who are planning a pregnancy or are currently pregnant or breastfeeding, due to factors that may impede completion of study procedures 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 as those for the healthy general population.

Practice Point 4.2.2.2: People with CKD G4–G5 (eGFR <30 ml/min per 1.73 m^2) 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 the safety data in this population are limited. One short-term trial that included 42 people with an eGFR >20 ml/min per 1.73 m^2 had 2 cases of reversible hyponatremia (Na <132 mmol/l; the eGFR of these 2 participants was, respectively, 28 and 57 ml/min per 1.73 m^2).[442] People with ADPKD should be assessed for clinical contraindications by the treating nephrologist. In the PREVENT-ADPKD study, participants who were at risk for developing hyponatremia, fluid overload, or urinary tract obstruction were excluded from the study. These conditions may include the following: people with a baseline serum sodium level <135 mmol/l; requirement for medications that have a high risk of precipitating hyponatremia, such as chronic use of diuretics, selective serotonin reuptake inhibitors, or tricyclic antidepressants; medical conditions that require fluid restriction, such as heart failure, chronic liver disease, nephrotic syndrome, or generalized edema; and abnormalities in the voiding mechanism.[257]

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 daily fluid intake at baseline can verify whether current fluid intake is adequate and can assist with subsequent education. No consensus has been reached on which methods should be used to estimate daily fluid intake in people with ADPKD.[444,445] Multiple methods are reported, with varying degrees of convenience to the person with ADPKD, resource utilization, and accuracy.[441] Dietary recall information (such as the number of cups of fluid, and the types of fluid, consumed per day) takes <5 minutes to obtain,

and a simple screen can be used to estimate fluid intake, but it is self-reported and is subject to underreporting or, more likely, overreporting. Self-administered semiquantitative beverage- and food-frequency questionnaires, such as the Beverage Frequency Questionnaire (BFQ; validated in people with ADPKD), provide a structured approach and may increase patient self-awareness, but they are also self-reported and are prone to misestimation.[446] Measurement of urine volume and osmolality from a 24-hour urine test provides the best method of estimating fluid intake and osmotic load, but it has the disadvantages of day-to-day variability in fluid intake, errors due to incomplete collections, and the inconvenience to people with ADPKD.

Although a daily water intake of approximately ≥2 l/d is recommended for people with ADPKD, in view of its kidney-protective benefits, the effect of high water intake on liver cyst progression remains to be investigated.

Research recommendations

Only one RCT has evaluated the long-term efficacy of increasing water intake on the progression of ADPKD. Further studies are needed, such as the following:

- 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 risk factor for progression; and
- interventional RCTs evaluating the combination of tolvaptan and water intake.

4.3 Mammalian target of rapamycin (mTOR) inhibitors

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

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.[446–450]

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 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 receive either placebo or everolimus (2.5 mg twice per day).[450] 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 the change was not significant at 2 years. The adjusted annual decline in eGFR was significantly faster in the everolimus group versus the placebo group (–5.5 ml/min per year vs. –3.5 ml/min per year, respectively; $P < 0.001$).[450] Other secondary endpoints (proteinuria and BP) were similar in both arms.[450] Although these data are highly imprecise, all-cause death (OR: 2.04; 95% CI: 0.18–22.67) and doubling of SCr level or incidence of kidney failure (OR: 5.26; 95% CI: 0.24–117) were more likely to occur in the everolimus group. Discontinuation due to adverse events (OR: 3.35; 95% CI: 1.83–6.14) was much more likely to occur in the everolimus group.[450]

The second-largest study by Serra *et al.* was an 18-month open-label trial in which 100 participants were randomized to receive either sirolimus (2 mg/d) or standard care.[448] The primary outcome (change in TKV at 18 months) did not differ between the 2 arms. In addition, the rate of decline in eGFR was similar in both arms, but the incidence of 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) was increased in the sirolimus arm, compared to that in the standard-care arm.

Stallone *et al.* examined the role of mTOR-inhibitor dose, and its combination with an ACEi, in a prospective 2-year open-label trial in which 55 people with a *PKD1* mutation were randomized to groups receiving either high-dose sirolimus plus ramipril, low-dose sirolimus plus ramipril, or ramipril alone.[449] The downstream target of mTOR activation, p70S6 kinase phosphorylation, was reduced in peripheral blood mononuclear cells in the sirolimus group. However, no significant change occurred 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 and severely abnormal kidney function who were randomized to receive either sirolimus (3 mg/d; trough, 5–10 ng/ml [5.5–11 nmol/l]) or conventional treatment.[447] No difference occurred 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 level or incidence of 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 in design, but overall, they had a low-to-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 to 2.6; $P < 0.1$). In addition, although the grade of certainty of evidence was low, sparse but strong associations with risk of harm due to adverse events occurred across all 4 studies. A meta-analysis consisting of 9 RCTs and 784 people with ADPKD, which had broader eligibility criteria than those for our review (e.g., inclusion of combination therapies) 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).[451]

Certainty of evidence. The overall certainty of evidence was graded as low, due primarily to some inconsistency in effect estimates across studies and sparse estimates of harms (Supplementary Table S17[447–450]). The trials for the most part had no serious methodological concerns, except that 1 trial had poor reporting of their study methods. The critical outcomes of CKD progression and TKV progression were reported most commonly, but the level of heterogeneity of treatment effects for both outcomes across studies was high (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 reported only sparsely, providing a very low certainty-of-effect level. 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. Because the effect estimates were large (OR $> \sim 2$), we concluded that the grade of certainty of evidence was low for these outcomes. Other important outcomes were not reported. Thus, based primarily on the low certainty-of-evidence grade for CKD incidence, TKV progression, and adverse-event incidence, we concluded that the overall grade of certainty of evidence is low.

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

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

Considerations for implementation. The clinical trials regarding mTOR inhibitors were conducted in people with European ancestry, but no evidence suggests that the conclusions would be different in other regions of the world, based on pharmacokinetic data.[452]

Rationale

Although preclinical studies in small animal models of PKD demonstrated that using high-doses of mTOR inhibitors suppresses the proliferation of cystic epithelial cells and reduces kidney cyst growth,[453] overall, 4 RCTs using conventional clinical dosing demonstrated no beneficial effects on primary endpoints of kidney disease progression. Moreover, the studies found significant increases in the incidence of 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.

Rarely, instances of deletions of both *TSC2* and *PKD1* causing a contiguous gene syndrome have been described, presenting primarily as clinical syndrome overlap characterized by early-onset polycystic kidney disease, together with typical manifestations of tuberous sclerosis.[90] Currently, data are limited on the risk-benefits of using mTOR treatment in this setting, and this area requires further study.[454–456]

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 their evaluation in clinical trials, is needed.
- A study to evaluate the safety and efficacy of mTOR inhibitors in the treatment of people with the rare TSC/PKD1 contiguous gene syndrome 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 Practice Guideline for Lipid Management in CKD*),[277] *currently, no evidence indicates 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, 1 in adults and 1 in children.[457,458] The trial in adults (with 49 analyzed participants) found no significant difference in eGFR between a pravastatin-treatment and a no-treatment group (net difference: −0.08; 95% CI: –0.71 to 0.56) at 2-year follow-up.[458] However, the trial was open-label, had a large loss to follow-up, and did not report an intention-to-treat analysis. The trial of 110 children randomized them to receive either a combination of lisinopril plus pravastatin (20–40 mg/d) or lisinopril plus placebo.[457] The primary outcome measure (rate of change in htTKV) was reduced in the lisinopril-plus-pravastatin group, compared to the lisinopril-plus-placebo group (net difference: –9%; 95% CI: –16% to –2%).[457] No participant discontinued treatment as a result of adverse events. Overall, based on the limited evidence of the 2 trials, no high-quality evidence indicates 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 use ($n = 85$) versus no treatment ($n = 438$).[459] Overall, no beneficial effects of statins, in reducing TKV or decline in eGFR, occurred.[459]

Certainty of evidence. The overall certainty of evidence was graded as very low for adults, due primarily to the fact that it came from only a single trial with serious limitations in adults (Supplementary Table S18[457,458]). The overall certainty of evidence was graded as low 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 a low grade of certainty of evidence for the critical outcome of change in TKV, but it had insufficient evidence regarding possible harms. Most prioritized outcomes were not reported by either study.

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

Resource use and cost. Statins are utilized universally for cardiovascular risk prevention, and this usage is the prime rationale for their indication in people with ADPKD. Although statins are available widely and at low cost, the evidence is currently insufficient 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 in slowing kidney disease progression in ADPKD is not known, and well powered, multicenter, clinical data are required to resolve this issue. Due to the limited amount of evidence, other clinical practice guidelines in ADPKD are consistent with recommendations made by the KDIGO Work Group.[460,461]

Rationale

The evidence to support the use of statins to slow kidney disease progression in people is limited to that from 2 clinical trials, neither of which demonstrated a benefit in reducing eGFR decline. A 2-year randomized, double-blind placebo-controlled, parallel study ($n = 200$; eGFR ≥60 ml/min per 1.73 m^2; NCT03273413) is in progress currently 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 PKD1 and PKD2 lead to abnormalities in intracellular signaling pathways that include the downregulation of adenosine monophosphate (AMP)-activation protein kinase. The antidiabetic drug metformin has pleiotropic actions that include the activation of adenosine monophosphate-activation protein kinase, 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 people with 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.[185,462–464] Brosnahan *et al.* reported a 12-month prospective double-blind trial of 51 participants who were randomized to receive either metformin (500–1000 mg twice daily) or placebo.[462] Metformin and placebo were tolerated by 82% and 100% of participants (primary endpoint), respectively, after 12 months, and no differences occurred in the secondary endpoints (change in TKV or in eGFR). The incidence of adverse events in the metformin group was increased, compared to that in the placebo group (OR: 4.11; 95% CI: 1.27–13.36). No indication was present of a difference in mild hypoglycemia (OR: 0.96; 95% CI: 0.06–16.23), but the estimate was highly imprecise, and no episodes of lactic acidosis occurred. Similarly, Perrone *et al.* reported the results of a 2-year double-blind RCT of 97 people with ADPKD allocated to receive either metformin (500–1000 mg twice daily) or placebo for 26 months.[185] The primary endpoint was tolerance of the study drug, and overall, 89% of those receiving metformin, and 81% of those receiving placebo met the adherence threshold of >50%. No intergroup differences occurred in eGFR decline or TKV increase. Finally, Chaudhary *et al.* reported an open-label trial of 70 people with ADPKD who were randomized to receive either metformin (0.5–1 g twice daily) or placebo over 12 months.[463] The primary outcome of 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 reduction was associated with improvements in secondary kidney outcome measures, including eGFR decline and proteinuria reduction, but minimal details that could be used to assess adverse events were reported.

Certainty of evidence. The overall certainty of evidence was graded as moderate, based on the high and moderate grades of certainty of evidence regarding CKD and TKV outcomes, and the low grade of certainty of evidence for an increase in the incidence of diarrhea (Supplementary Table S19[185,462,463]). The 3 eligible trials had no serious methodological concerns, although one was open-label. The critical outcome of CKD progression had a high grade of certainty of evidence, without serious concerns about the evidence. The critical outcome of TKV progression had a moderate grade of certainty of evidence, due to some inconsistency across studies. The evidence for other critical outcomes either was sparse (and for pain, imprecise) or was not reported. One study provided a low graded of certainty of evidence for risk of diarrhea, with a large effect size. Data on other important outcomes were sparse and imprecise, or were

not reported. Based primarily on the grades of high and moderate for certainty of evidence for the critical outcomes of CKD and TKV progression, together with the low grade of certainty of evidence for diarrhea, we concluded that the overall grade of certainty of evidence is moderate.

Values and preferences. Metformin has a favorable safety profile that is validated by over 50 years of clinical use for other chronic conditions.[465] This finding suggests that long-term clinical trials in people with ADPKD may be conducted safely to determine if metformin use slows progression of kidney disease.

Resource use and cost. As a repurposed drug, metformin has wide availability, is low in cost, and is accessible, providing considerable potential for its use in 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 that in the 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) presently underway.

Rationale

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

Research recommendation

- A long-term RCT comparing use of metformin versus placebo in people with ADPKD and CKD G2–G3b is needed.

4.6 Somatostatin analogues

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

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

Somatostatin is an endogenous hormone that suppresses intracellular cyclic adenosine monophosphate synthesis, and therefore, it has been hypothesized to reduce kidney cyst growth.[466] The short half-life of endogenous somatostatin has led to the repurposing of somatostatin analogues (octreotide, lanreotide, pasireotide) for evaluation in ADPKD clinical trials.[466] 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, these drugs may have a place 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.[467–469] For instance, the A Long-Acting somatostatin on DIsease progression in Nephropathy due to 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 the primary endpoint.[467] 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 from baseline to year 3 was not significantly different in the octreotide LAR group compared to that in the placebo group, 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 the drawing of conclusions complicated. 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 m^2), with TKV growth and measured GFR decline as the primary endpoints.[469] In this study, octreotide LAR significantly reduced TKV growth at 1 and 3 years, but no significant effect on measured GFR decline occurred (neither when measured as slope from baseline to year 3, nor when measured as slope from year 1 to 3). Despite the lack of effect on measured GFR decline, people treated with octreotide LAR progressed less frequently to a composite endpoint of doubling of SCr level, or kidney failure, compared to the placebo group (17.6% vs. 42.9%, respectively). This composite endpoint, however, was not defined *a priori* (NCT00309283). Later, a much larger study (Developing Interventions to Halt Progression of ADPKD [DIPAK-1])[468] that randomized 309 people with ADPKD to receive either the somatostatin analog lanreotide or standard treatment found no significant effect of lanreotide on the primary outcome rate of eGFR decline (−3.53 ml/min per 1.73 m^2 per year vs. −3.46 ml/min per 1.73 m^2 for the placebo group), nor on the incidence of the combined endpoint of worsening of kidney function (defined as a 30% eGFR decrease or the 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 htTKV growth rate at week 120 (end-of-treatment) was −2.14% per year (95% CI: –3.14% to 1.12%; $P < 0.001$), with a rate of TKV growth of 3.55% versus 5.81% per year in the lanreotide versus the control group, 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.[470] Of note, the effect of the somatostatin analog on volume growth of the polycystic liver and kidneys is biphasic, consisting of a strong short-term decrease and a long-term, chronic treatment effect.[468,470] After 2.5 years of treatment, when the somatostatin analog was stopped, the chronic effect largely remained.[468] Lastly, the Lanreotide In Polycystic kidney disease (LIPS) study also investigated lanreotide using kidney function as a primary outcome in 159 people with ADPKD.[471] This study was completed in 2019, but publication of the results is still awaited (NCT02127437). Besides these 4 studies, which had relatively long treatment durations, several other shorter-term studies have been performed, such as those by Hogan *et al.* and van Keimpema *et al.*[471,472] In general, the results of these studies align with those of 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. Aside from their general side effects, such as causing gastrointestinal discomfort, hyperglycemia (especially with the pan-somatostatin receptor analog pasireotide), and bradycardia,[466] they may have 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,[473] and gallstone formation has been noted with lanreotide, as compared to control treatment,[474] with associated biliary complications, such as cholecystitis and pancreatitis.[474] 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 grade for the critical outcomes of CKD progression, TKV progression, and incidence of serious adverse events, supported by the low grade of certainty of evidence for other outcomes (Supplementary Table S20[467–470,472,473,475–477]). The 5 RCTs had some limitations related mostly to lack of blinding or to a high rate of missing data, and possible selective reporting. In addition to the moderate grade of certainty of evidence for the critical outcomes noted above, the grade of certainty of evidence was low for the critical outcomes, other adverse events (liver cyst infections, gallstones, other gastrointestinal issues), and QoL, due to the sparseness of evidence (1 study per outcome). The grade of certainty of evidence was very low for the critical outcome of pain, due to its sparseness and imprecision. Based primarily on the moderate grade of certainty of evidence for CKD and TKV progression, and the moderate and low grades of certainty of evidence for various adverse events, we concluded that the overall grade of certainty of evidence is moderate.

Values and preferences. Although somatostatin analogues do not have clear beneficial effects on reducing eGFR decline, these agents may play a role in reducing volume-related complaints in ADPKD that are due to the kidney and liver (see also Chapter 5).[478] 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 of 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.[474]

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 the benefits relating to preventing kidney failure, thereby limiting the potential for 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 be considered in only those people with severe complaints due to their having massively enlarged polycystic organs, due to the kidney and liver (see also Chapter 5). In addition, trying 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) seems prudent. In cases in which no beneficial effects are observed, medication should be withdrawn.

Rationale

Overall, analysis of the 5 RCTs of somatostatin analogues showed that they had 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 portion of the effect on TKV was maintained 3 months after the drug was stopped. 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 be considered in only selected people who have severe symptoms secondary to massive kidney enlargement, and for whom the benefit of treatment may outweigh the potential harms.

Overall, somatostatin analogues should not be prescribed to improve the rate of eGFR loss in people with ADPKD, but they can be considered for improving symptoms in people who have severe symptoms from large polycystic kidneys and liver (see Chapter 5).

Research recommendations

- Differences in kidney-protective efficacy may occur among the various somatostatin analogues, with octreotide potentially having a greater effect. For this reason, an adequately powered long-term RCT could be considered that compares octreotide use to receipt of placebo in people with ADPKD and rapidly progressive disease. The primary endpoints of this trial should be defined *a priori* and should

include the rate of eGFR change during treatment, as well as the effect on QoL in people with severe complaints related to their having massively enlarged polycystic organs.

4.7 Sodium-glucose co-transporter-2 inhibitors (SGLT2i)

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

SGLT2i block the sodium-glucose co-transporter 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 central vasopressin release, which has been involved in cystogenesis and progression of ADPKD.

Recent studies have demonstrated that SGLT2i have a kidney-protective and cardioprotective effect in both people with and without diabetes. The potential benefits of SGLT2i have not been explored specifically in ADPKD, because the major trials of SGLT2i in CKD without diabetes 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.[291,479,480] Current data in humans are observational.[481,482] An RCT that is underway will evaluate the safety and potential efficacy of SGLT2i in people with ADPKD (NCT05510115). Research also is needed to understand the metabolic effects of SGLT2i in this population.

Research recommendations

- Studies are needed to evaluate the safety, efficacy, and metabolic effects of SGLT2i use in people with ADPKD.

4.8 Ketogenic interventions

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

Ketogenic interventions include both diets that induce ketosis, and treatment with ketone supplements. The hypothesis has been proposed that switching the cellular fuel source from glucose to ketone bodies will reduce kidney cyst growth. Cells with mutations in PKD genes are reprogrammed metabolically and depend on glucose as an energy source (through aerobic glycolysis) instead of oxygen (through oxidative phosphorylation).[483] Results from preclinical studies in PKD,[136,138,484] combined with the popularity of self-management of obesity, have sparked substantial interest in whether interventions that induce long-term ketosis through dietary modification, intermittent fasting, or ketone body supplementation (such as β-hydroxybutyrate) are beneficial in people with ADPKD.[485,486]

The efficacy and safety of ketogenic interventions (via diets that induce ketosis, and/or treatment with ketone supplements) have been established in ADPKD only in short-term trials, and not in long-term trials looking at disease progression. To date, the following 4 small studies have been conducted: Testa *et al.* was a single-arm pilot study of $n = 3$ of a modified Atkins Diet for 3 months[487]; a retrospective case-series study by Strubl *et al.* used self-report by participants ($n = 131$) for 6 months ($n = 74$ on a ketogenic diet; $n = 52$ on time-restricted feeding for 6 months), and was subject to bias[488]; Oehm *et al.* was a small, single-arm study, with $n = 5$ on water fasting, and $n = 5$ on a ketogenic diet[489]; and Cukoski *et al.* was an RCT ($n = 63$) with 3 arms—those on a ketogenic diet, those on water fasting, and a control group, for 3 months.[490] Different methods of implementing ketogenic diets are also available, including plant-based approaches.[491]

The long-term safety and efficacy of these interventions in people with ADPKD have not been established, and therefore, they should not be implemented. Potential safety risks include hyperlipidemia and hypercalciuria and nephrolithiasis.[492] Similarly, although preclinical data have suggested that lithogenicity mediates disease progression in PKD,[138] its specific efficacy in people with ADPKD has not been evaluated.

Research recommendations

- Large, long-term (several years) RCTs are needed to determine the efficacy and safety of the ketogenic diets and/or β-hydroxybutyrate supplementation in relation to known risks, such as hyperlipidemia and nephrolithiasis.[493]
- Observational cohort studies are needed to evaluate the effects of urinary oxalate levels and dietary oxalate intake on disease progression.

4.9 Complementary medicines

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

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 on the basis of information obtained from a broad range of sources. Presently, no evidence indicates that specific types of complementary medicines slow kidney disease progression in people with ADPKD, and little to no information is available about potential harms. However, this lack of availability is due to the fact that very little research has been undertaken in this field.

To date, only 2 clinical trials have been conducted that involved niacinamide and curcumin. In general, the studies have been small and underpowered, and overall, no beneficial effects on ADPKD progression were demonstrated. Although

most complementary medicines available in settings with a high level of resources have been assessed by regulatory authorities and may be considered to have a low risk of harm at recommended dosages for people who are generally healthy, many others are available via online purchasing. The quality and safety of these is therefore uncertain, and their potential harms in people with CKD in general and ADPKD specifically is unknown. Due to the uncertainty and paucity of the evidence, use of complementary medicines or supplements is not advisable in people with ADPKD.

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.[494] The phenotype may be restricted to the liver, but PLD also may occur in conjunction with kidney cysts in ADPKD. For research purposes, each of the following phenotypic characteristics have been used to assign the diagnosis of PLD: (i) the presence of any liver cyst when it occurs in association with ADPKD[495]; (ii) the presence of 1 cyst before aged 40 years, or 4 cysts after aged 40 years in families with PLD with no or only a few kidney cysts (ADPLD)[496]; and (iii) in the presence of >10 liver cysts (or >20 liver cysts, as specified in other publications) in the absence of a family history of ADPKD or ADPLD.[494,497] This chapter addresses ADPKD-related PLD. Although the majority of people with ADPKD have liver cysts, and the prevalence of liver cysts increases with age, most people will not develop clinically symptomatic PLD.[498] The presence of liver cysts, even in advanced PLD, usually does not impact the synthetic or secretory capacity of the liver. However, symptoms can ensue that are related to the mass effect of a large cystic liver exerting pressure on the diaphragm and abdominal wall, thereby compressing other abdominal organs and vascular structures.

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

Multiple classifications for PLD have been proposed that are based on liver volume and cyst characteristics (Table 12).[499–502] The first proposed staging systems were aimed at identifying people eligible for cyst volume–reduction surgery or liver transplantation, based on cyst number, size, and distribution.[500,501] Afterward, staging systems were proposed that aimed to classify disease severity, based on cyst number and liver volume.[498,499,502] Liver volume correlates with the presence and severity of symptoms in PLD.[503] Therefore, total liver volume (TLV) should be evaluated whenever abdominal imaging is performed, to assess disease severity in ADPKD. Two studies used height-adjusted total liver volume (htTLV) for this purpose, but they used different thresholds: PLD was classified in 1 study as mild, moderate, or severe with htTLV thresholds of <1600 ml/m, 1600–3200 ml/m, and >3200 ml/m, respectively, whereas the other (the HALT-PKD study) used different htTLVs (mild, <1000 ml/m; moderate, 1000–1800 ml/m; and severe, >1800 ml/m).[495,499] A major limitation of all previously described classification systems is that they do not factor in the age of the person. Recently, the HALT study and CRISP PKD study investigators proposed a classification that is based on height-adjusted liver cyst volume (htLCV), adjusted for age.[504] HtLCV growth was calculated from a nonzero theoretical starting point, and people were grouped according to their annual htLCV growth, as follows: class A, <5%; class B, 5%–10%; class C, 10%–15%; class D, 15%–20%; and class E, >20%. People with a substantial liver cyst burden (in 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.

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 do kidney cysts. Liver cysts are eventually seen in 90% of people with ADPKD, typically are more numerous and larger in women than in men, and typically remain asymptomatic throughout life.[498,506] 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 a liver transplant, is unlikely to occur. Although liver dysfunction is extremely unlikely to occur as a result of PLD, manifestations of hepatomegaly may affect QoL. The presence of resulting symptoms, such as abdominal pain, early satiety, acid reflux, shortness of breath, weight loss, and loss of appetite, should be communicated to the attending 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, an increased kidney or liver cyst burden will cause symptoms when adjacent structures, including the 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 originating from causes unrelated to PLD (e.g., irritable bowel syndrome, kidney stones or gallstones, small intestinal bacterial overgrowth, and diverticular disease of the colon).

Abdominal wall and diaphragmatic hernias, and gastroesophageal reflux, are often present, whereas other complications of PLD are rarely observed.[507] Rare complications may cause symptoms when cysts compress the inferior vena

Table 12 | Classifications for PLD

Staging system	Classes	Aim of the system	Limitation
Gigot *et al.* 1996[500]	• 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 and/or liver growth • No information regarding prognosis
Schnelldorfer *et al.* 2009[501]	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 to 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 • Areas of relative normal liver parenchyma: <1 sector • Isosectoral portal vein or hepatic vein occlusion of preserved sector: present	Patient selection for volume-reducing therapy and liver transplantation	• Did not factor in age and/or liver growth • No information regarding prognosis
Qian *et al.* 2003[502]	• 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 and/or liver growth • No information regarding prognosis
Kim *et al.* 2015[499]	• Mild: htTLV <1600 ml/m • Moderate: 1600 ≤ htTLV <3200 ml/m • Severe: htTLV ≥3200 ml/m	Determination of disease severity	• Did not factor in age and/or liver growth • No information regarding prognosis
Hogan *et al.* 2015 (HALT-PKD)[495]	• Mild: htTLV <1000 ml/m • Moderate: htTLV between 1000 and 1800 ml/m • Severe: htTLV >1800 ml/m	Determination of disease severity	• Did not factor in age and/or liver growth • No information regarding prognosis
Bae *et al.* 2022 (HALT-PKD and CRISP)[504]	• Class A: htLCV annual growth <5% • Class B: htLCV annual growth 5%–10% • Class C: htLCV annual growth 10%–15% • Class D: htLCV annual growth 15%–20% • Class E: htLCV annual growth >20%	Determination of disease severity	• Not validated in independent populations
Sierks *et al.* 2022[505]	Normalized age-adjusted liver volume • Progression Group 1: <3.3% annual growth • Progression Group II: 3.3%–6.6% annual growth • Progression Group III: >6.6% annual growth	Individual prognostication	• Not validated in independent populations • Normalized against a standard baseline liver volume of 850 ml/m at age 20 yr (fold-over standard baseline TLV at age 20 yr = htTLV)

CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; HALT-PKD, HALT Progression of Polycystic Kidney Disease; htLCV, height-adjusted liver cyst volume; htTLV, height-adjusted total liver volume; PLD, polycystic liver disease.

cava (lower-extremity 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, and MRI may aid in the differentiation and identification of the origin of pain (e.g., kidney, liver, or other adjacent structures). Although CT and MRI provide more precise imaging, ultrasound can be useful as an initial imaging tool to sort out potential causes for the symptoms.[494,508]

Typically, liver function remains unaffected in people with PLD, even in the most severe cases. Occasional elevations in levels of alkaline phosphatase and gamma-glutamyl transferase may be observed, but they have no clinical consequence.[509,510] 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) do not need periodic testing 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 affected, and symptoms can be grouped as follows (Figure 31):

- overall liver size;
- pressure against diaphragm and lungs;
- pressure against the stomach; and
- cyst complications
  - intracystic
  - extracystic.

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.[511] However, general QoL questionnaires lack disease specificity to adequately capture PLD-related symptom burden. Two disease-specific symptom questionnaires, the PLD-Q and the POLCA, have been developed and validated.[512,513] The PLD-Q accurately and reliably assesses PLD symptom severity and is used to evaluate treatment efficacy for PLD-related treatments.[472,514,515] 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 sex, liver volume and/or 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 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 counseled about the benefits and potential harms of sex hormone therapy.

Women with ADPKD are more often affected with PLD (>80%) than are men.[509] This difference 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, compared to PLD in men. Approximately 85% of people with ADPKD and symptomatic PLD presenting for medical care are women. TLV is, on average, greater in women than it is in men, and >80% of liver transplantations performed for symptomatic PLD occur in women.[516]

An age-dependent growth pattern of PLD occurs in people with ADPKD. In women aged <48 years, the median liver growth is 2.65% per year, compared to 0.09% per year in those aged ≥48 years. This demarcation in age appears to

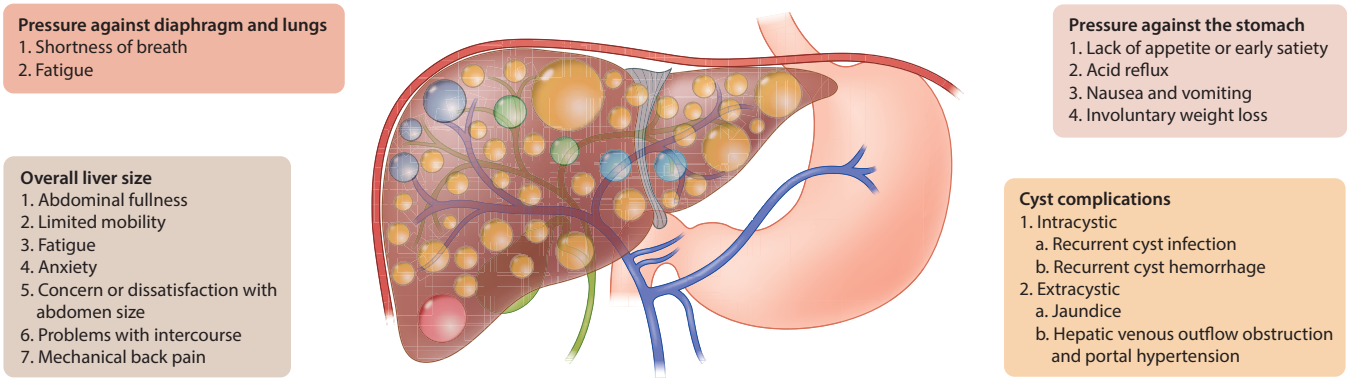


Figure 31 | Symptoms of polycystic liver disease. Uncomplicated cysts (yellow); recurrent cyst infection (gray); recurrent cyst hemorrhage (red); cyst obstructing the bile ducts (green); and cysts obstructing hepatic veins (blue).

coincide with menopause and may support the concept that an aggressive, premenopausal TLV growth pattern occurs that lessens after menopause.[517]

Observational studies have demonstrated that yearly exposure to estrogen-containing oral contraceptives is associated with a 1.45% greater TLV in women with ADPKD (a 15.5% greater TLV for each decade of use).[518] A case–control study of 19 postmenopausal women with ADPKD and PLD demonstrated that estrogen replacement therapy was associated with a 7% annual increase in TLV, whereas those not receiving estrogen replacement therapy demonstrated a 2% annual decline in TLV.[519] One study suggested that a relationship exists between number of pregnancies and PLD severity, but this observation has not been validated.[516] The role of pregnancy in ADPKD and its relation to PLD are 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, and estrogen- or progesterone-based intrauterine devices [IUDs]) 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 instead should adhere to diet and lifestyle advice geared 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 (Table 13).

Malnutrition is an important complication of PLD.[520,521] Malnutrition results primarily from the mass effect of TLV, which 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.[513] Symptoms result in an inadequate intake of nutrients, weight loss, and sarcopenia, which is seen frequently in people with severe hepatomegaly.[520,521] Small, frequent meals dictated by having multiple (e.g., 6–10 meals) episodes of eating small amounts, throughout the day, is the best strategy to cope with symptoms of early satiety. 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 13). Measurement of the skeletal muscle index in a single CT slice at the third lumbar vertebra is the most accurate method to diagnose sarcopenia.[522] Nutritional status and malnutrition can be assessed

Table 13 | Methods to assess sarcopenia and malnutrition

Technique	Definition of sarcopenia or malnutrition
Skeletal muscle index	• Skeletal muscle mass measured at 3rd lumbar vertebrae. Sarcopenia defined as SMI <38.5 cm^2/h^2 in female patients, and <52.4 cm^2/h^2 in male patients

Bioelectrical impedance analysis	• Sarcopenia:
	  • <5.7 kg/m^2 in female patients
	  • <7.0 kg/m^2 in male patients

Grip strength	• Sarcopenia:
	  • Female patients, <18 kg
	  • Male patients, <26 kg

Mid-arm circumference	• Severe malnutrition:
	  • Female patients: <23.1 cm
	  • Male patients: <23.8 cm

Detailed nutritional assessment	• Includes: clinical examination (history and physical examination), anthropometric measurements, diagnostic tests (laboratory tests and body composition studies) and dietary assessment

SMI, skeletal muscle index.

with bioelectrical impedance analysis, grip strength, mid-arm circumference, and detailed nutritional assessments by nutritionists.[523] Weight loss and 24-hour calorie counts also can be used as general markers of nutritional status.

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.[520] Sarcopenia serves as an important criterion for liver transplantation in PLD in the setting of normal liver function, which complicates the proper use of traditional Model for End-stage Liver Disease (MELD)-based liver allocation.[524] However, a person's nutritional status, including sarcopenia, negatively impacts survival after liver transplantation, and prehabilitation in preparation for liver transplant is advised.[525–527]

People with sarcopenia and PLD often consume small portions of food spread throughout the day. No data are available examining the effects of diet and exercise interventions on sarcopenia status. However, current literature consistently shows that sarcopenia negatively impacts outcomes after liver transplantation.[525–527] 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 5.2.3.1: Treatment for PLD should be performed in centers of expertise.

Sufficient expertise with the treatment of people with PLD is required to minimize the risk of complications from surgery for PLD and manage the side effects of therapy. Surgery for PLD may be complicated in view of the variety of anatomic 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 also should be performed in centers of expertise, to prevent exposing patients to complications and side effects of ineffective PLD treatment options (Table 14).

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.

Given that 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 pharmacologic, interventional radiology, and surgical means, depending on cyst characteristics and the availability of experience at the medical center.[494,528]

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

Interventional radiologic therapies include aspiration sclerotherapy and transarterial embolization of hepatic arteries (Table 14). The expertise of the interventional radiologist performing these procedures is critical to ensure their safety and success.

Aspiration sclerotherapy is performed in people with one or a 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.[529,530] Various sclerosing agents have been used, without evidence for the superiority of any of these agents.[529] The final result is achieved approximately 3–6 months after the procedure, and we advise against reintervention in the first months postprocedure. Usually, cysts measuring ≥5 cm in diameter are amenable to successful sclerotherapy. Large cysts may require additional measures, such as increasing the dose of sclerosant, increasing the instillation time, or repeating a sclerotherapy treatment. The procedure is considered safe, and has limited side effects (mostly postprocedural pain), without reported mortality.

Transarterial embolization. The evidence for transarterial embolization of liver cysts is limited to results from case-series studies. This procedure is performed in a few centers in Japan, Korea, and France. The procedure requires hospitalization for 3–5 days for pain control, and prevention and treatment of postembolization syndrome. The procedure results in a mean reduction in liver volume of 13% at 3 months, and 28% at 51 months, with a reported symptomatic improvement in approximately 70% of people.[531,532]

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 to ensure 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.

Table 14 | Treatment options in PLD

Treatment option	Liver phenotype	Efficacy	Morbidity and mortality
Aspiration sclerotherapy (systematic review of 16 studies, 526 people with hepatic cysts)[529,530]	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	• Symptomatic improvement: 72%–100% • Cyst volume reduction: 76%–100%	• Minor complications: 5%–90% • Mortality: <1.0% (not reported)
Transarterial embolization (2 retrospective studies, 40 people with PLD)[531,532]	Diffuse symptomatic liver cysts with at least one segment of functioning liver remaining intact and no indication for alternative treatment options	• Symptomatic improvement: 72%–93% • Need for reintervention: 15% • Mean reduction in TLV: 13% at 3 mo, 28% at 51 mo	• Postembolization syndrome: 100% • Complications: 7.5% • No major complications
Laparoscopic cyst fenestration (metanalysis of 15 studies, 146 people with PLD)[515]	Large liver cysts located anteriorly and caudally	• Symptomatic recurrence: 33.7% • Need for reintervention: 26.4%	• Complications: 29.3% • Clavien-Dindo III–IV perioperative complications: 7.2% • Mortality: 2.3%
Combined partial hepatectomy and cyst fenestration (retrospective, single center, 186 people with PLD)[501,533,534]	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	• Median reduction in TLV: 61% postoperative and at 8 yr • Symptomatic improvement: 94%	• Clavien-Dindo III–IV perioperative complications: 21% • Mortality: 2.7% • Survival: 96%, 93%, 86%, and 78%, at 1, 5, 10, and 15 yr, respectively
Liver transplantation (2 retrospective reviews of 271 and 58 people with PLD)[536,537]	Massive PLD and (1) high symptom burden or, (2) sarcopenia or, (3) PLD-related complications, and a contraindication or failure of alternative treatment options[467]	Only curative treatment option	• Postoperative complications: 46% • Mortality: 9% • 1-yr patient survival: 85%–95% • 5-yr patient survival 77%–92%
Somatostatin analogues[470,472,538,539]	People with volume-related symptoms	• Reduction TLV growth rate by –6.37% within 1–3 yr of follow-up[478]	• 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 • Increased risk of gallstones • Bradycardia • Rarely liver cyst infections in patients with a previous history of cyst infections

PLD, polycystic liver disease; TLV, total liver volume.

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 patients. This surgical approach comes with a higher incidence of morbidity and mortality, compared to that with aspiration sclerotherapy.[515]

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.[501,533] This surgery is technically challenging and should be performed only in centers of expertise. This procedure is associated with a greater complication rate, a longer operative time, and a greater amount of blood loss, compared to those with 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 greatest impact seen on the symptoms of early satiety and dyspnea.[534] QoL also improved. In the largest series of people ($n = 186$) published to date, PHCF led to a significant decrease in liver volume (–61%), but major perioperative complications (Clavien-Dindo III/IV, i.e. requiring surgical, endoscopic, or radiologic intervention or ICU management) occurred in 21% of the people, and operative mortality (<90 days) occurred in 2.7%.[535] Eleven people eventually had liver failure, received liver transplants, or died from liver related causes. Because previous liver surgery and development of adhesions increase the difficulty of performing liver transplantation, PHCF should be considered in patients for whom long-term satisfactory results are anticipated and not in those who likely will require liver transplantation.

Liver transplantation is the only curative intervention for PLD and is discussed below.

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

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

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

This recommendation places a high value on the reduction in TLV and TKV, and the prevention of the need for 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′- cyclic adenosine monophosphate 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.[470,472,538,539] These trials provide a moderate certainty of evidence that somatostatin analogues reduce TLV in people with ADPKD and ADPLD, as compared to placebo. Somatostatin analogues also reduce the rate of growth of polycystic kidneys but do not slow the rate of eGFR decline.[467,468] Adverse events included mild gastrointestinal symptoms (e.g., steatorrhea, and transient abdominal cramps), cholelithiasis, hypo- and hyperglycemia, and alopecia.[540] Hyperglycemia and diabetes are more common with pasireotide than they are with lanreotide and octreotide.[472] An individual patient meta-analysis demonstrated that young women benefit the most from somatostatin analogues.[541]

Certainty of evidence. The overall certainty of evidence was graded as moderate (Supplementary Table S21[470,472,475–477]). Four RCTs, most with a 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 of liver size, providing a moderate grade of certainty of evidence. One small study provided sparse evidence, and thus a very low grade of certainty of evidence, for the critical outcomes of pain and QoL, and several important harms. The trials did not evaluate other critical outcomes. Therefore, overall, the grade of certainty of evidence was moderate, 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 the reversibility of side effects of the therapy. A special emphasis also was placed on preventing the need for 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. Whether the effects of various specific somatostatin analogues differ is unknown, particularly those of octreotide LAR versus lanreotide.[466] Pasireotide does not appear to be more effective, whereas the incidence of adverse effects (e.g., hyperglycemia and diabetes) from it is more common.[472]

The effect of somatostatin analogues on the volume of polycystic liver and kidneys, as well as symptom burden, should be evaluated after 6 months of treatment. Therapy should be discontinued if inhibition of liver growth is not 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 a moderate grade of certainty of evidence that somatostatin analogues reduce total liver and kidney volume in PLD. Somatostatin analogues should be used in only symptomatic people with large polycystic livers, in view of the potential side effects and associated costs.

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

Medical alternatives to somatostatin analogues have been investigated. Preclinical studies demonstrated that ursodeoxycholic acid targets cyclic adenosine monophosphate in cystic cholangiocytes and reduces cholangiocyte proliferation.[542] However, a single clinical trial found that ursodeoxycholic acid does not reduce TLV in people with PLD.[543]

mTOR inhibitors used after kidney transplantation appeared to decrease TLV in a cohort study,[324] but this effect was not observed in a short-term RCT that compared octreotide monotherapy with octreotide-plus-everolimus treatment in nontransplanted people with PLD.[544] In addition, mTOR inhibitor–related toxicity impedes its application for PLD in clinical practice.

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).[547] V_2 receptor antagonists directly affect intracellular cyclic adenosine monophosphate levels in the kidney tubular cells expressing the V_2 receptor and are a potential treatment for PLD. The previous longstanding thinking was that V_2 receptors are absent from cystic cholangiocytes, but a recent study discovered V_2 receptors in both animal and human

cholangiocytes.[545] In addition, a case report describes drastic TLV reduction in a person who used a V_2 receptor antagonist.[546] However, no interventional trials have been conducted in people with PLD. Therefore, currently, these drugs should not be used solely to inhibit liver cyst growth.

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

Liver transplantation is the only curative treatment for PLD.[494] People with PLD comprise 1.5% of the liver transplantations currently performed worldwide. Outcomes after transplantation are excellent, with high patient- and graft-survival rates (patient survival at 1 year, 85%–95%, and at 5 years, 77%–92%; graft survival at 1 year, 94%, and at 5 years, 88%)[536,537]; 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.[524] Given that disease severity of PLD is not reflected by the established organ-allocation systems, people with PLD often are selected to undergo transplantation based on exception criteria, which vary from country to country.[508,548–550]

The most important parameters that establish an indication for liver transplantation in people with PLD are as follows: (i) the presence of massive PLD in combination with (ii) low QoL, (iii) sarcopenia or PLD-related complications, and (iv) contraindications or failure of alternative treatment options. 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.[513,551] Sarcopenia may be assessed with various methods, of which the CT-based skeletal muscle index is the most reliable. Malnutrition also can be assessed through a variety of standard measurements. An important complication that may hasten the need for liver transplantation is recurrent, refractory liver cyst infection, or hepatic vein obstruction.[552] PLD-related pitfalls regarding liver transplantation are illustrated in Figure 32.

Alternative treatment options should be explored by patients and physicians before liver transplantation is considered, given 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 the risk of tearing fragile liver or caval veins is increased, which may result in massive blood loss and intraoperative death. The procedure can be further complicated by postoperative bile leakage, bile duct stenosis, and/or 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 5.2.3.7: People with PLD should be referred for combined kidney–liver transplantation when an indication for liver transplantation is present and the person has severely impaired kidney function (eGFR of <30 ml/min per 1.73 m^2).

In people with ADPKD and an indication for liver transplantation with severely impaired kidney function (eGFR of <30 ml/min per 1.73 m^2), referral for combined kidney–liver transplantation is advised. Because eGFR may overestimate the level of kidney function in people with malnutrition, direct GFR measurements should be considered in people with borderline eGFR (30–45 ml/min per 1.73 m^2). 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.[553,554]

Research recommendations

- Studies are needed to identify people who are 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 is needed comparing aspiration sclerotherapy and cyst fenestration, to establish the relative efficacy and safety of these procedures.
- Studies are needed to determine the effect of somatostatin analogues on symptom severity and presence of side effects of treatment.

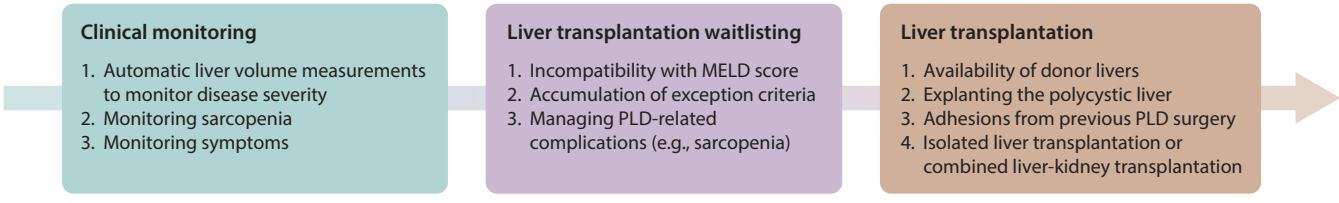


Figure 32 | Polycystic liver disease (PLD)-specific pitfalls in liver transplantation. "Automatic liver volume measurements" stands for a special image-processing approach.[150] MELD, model for end-stage liver disease.

- Studies are needed to investigate new medical alternatives for the treatment of symptomatic PLD.
- Studies are needed to evaluate the impact of V_2 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).

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 who are on dialysis and who are post–kidney transplantation 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 are positive in approximately 60% of liver cyst infections[555] and always should 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 (PET) with ^{18}F-fluorodeoxyglucose (FDG) PET-CT is a supportive item in the diagnostic algorithm and has 89% sensitivity and 75% specificity, a positive predictive value of 84%, and a negative predictive value of 82%.[556] 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 geographic regions.

A cyst aspirate showing neutrophils or bacteria is the gold standard to diagnose liver cyst infection.[557,558] The level of specificity of this test is high, but the test has a high false-negative rate, resulting in a low NPV. Therefore, a diagnostic algorithm was developed that provides an accurate

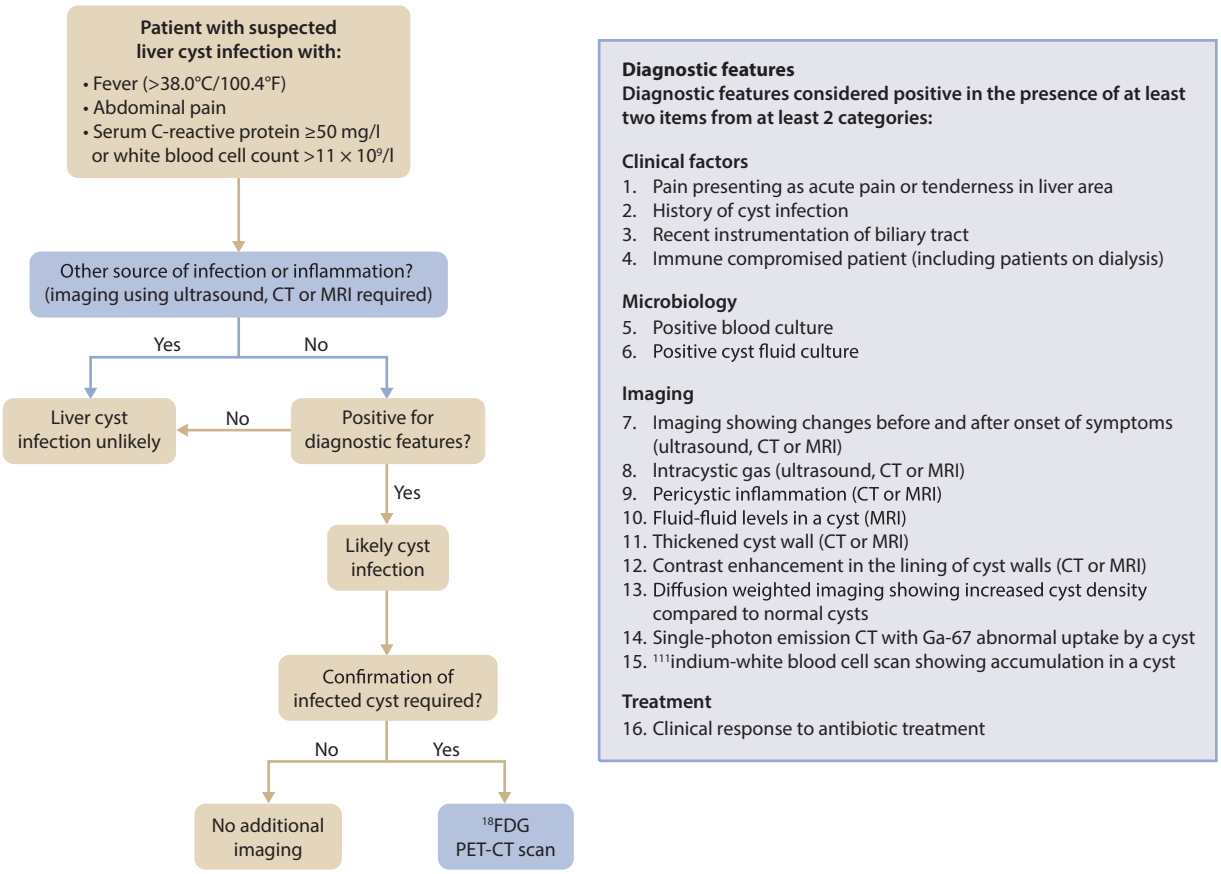


Figure 33 | Diagnostic algorithm to diagnose liver cyst infections in autosomal dominant polycystic kidney disease. CT, computed tomography; ^{18}FDG PET-CT, positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with computed tomography; Ga-67, Gallium-67; MRI, magnetic resonance imaging. Adapted from Lantinga *et al.*[269]

diagnosis of liver cyst infection, with a high level of consensus among experts in the field of ADPKD and PLD (Figure 33).[269]

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

Liver cyst infection should be distinguished from liver cyst hemorrhage. Both may present with localized liver pain; clinical, laboratory, and imaging findings may be used to differentiate between the 2 entities.[558] Cyst hemorrhage may be accompanied by elevations in body temperature, but these are rarely >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.[494,559] Antibiotics provide no beneficial effect in cyst hemorrhage. People with cyst hemorrhage should be treated symptomatically, with adequate pain relief. In liver cyst infections, fever and elevated acute-phase parameters (CRP level and leukocytosis) are observed. The radiologic features associated with liver cyst infections (e.g., altered cyst density, thickened and/or enhanced cyst walls) are not specific and should be used in combination with the diagnostic algorithm.[560,561] Application of the diagnostic algorithm (Figure 33) yields an approach to the diagnosis of liver cyst infection that helps prevent unnecessary exposure of patients to antibiotics.

5.3.2 Management

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

Liver cyst infection is a serious complication that may lead to sepsis and death if it is not treated adequately in a timely fashion. Thus, antibiotics should be administered as soon as possible after diagnosis (Figure 34). Liver cyst infections are caused most frequently by gram-negative bacteria from the *Enterobacteriaceae* family originating from the gastrointestinal system.[562,563] This bacterial family includes, among others, *Escherichia spp.*, *Klebsiella spp.*, *and Salmonella spp. 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 empirical treatment of liver cyst infections should be targeted primarily at gram-negative bacteria in the *Enterobacteriaceae* family.

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

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, whereas data from kidney cysts indicate that higher intracystic drug levels may be achieved with TMP-SMX.[564–566] In clinical practice, the highest level of treatment efficacy is obtained with third-generation cephalosporins (in case of low risk of extended-spectrum beta-lactamase presence) and fluoroquinolones (ciprofloxacin).[567] Antibiotic monotherapy is not always successful, and a recent literature review suggests that combining antibiotics may lead to superior treatment outcomes.[567,568] Antibiotic-resistance patterns vary across geographic 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.[569] When treating liver cyst infections, physicians also should take into consideration the side effects of antibiotics and the method of administration. Currently, antibiotics are administered systemically (with i.v. or oral delivery), and no studies have investigated alternative administration methods (e.g., instillation or flushing of cysts with antibiotics). Physicians also should be mindful of side effects associated with (long-term) antibiotic use (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, to which cysts >8 cm in diameter are less likely to respond without supportive cyst aspiration.

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

The appropriate 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.[508,567] At the physician's discretion, extending the course of antibiotics may be appropriate, 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); drug removal by dialysis also needs to be considered. These issues require person-specific tailoring of antibiotic regimes and monitoring of antibiotic drug levels whenever possible.[570] 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

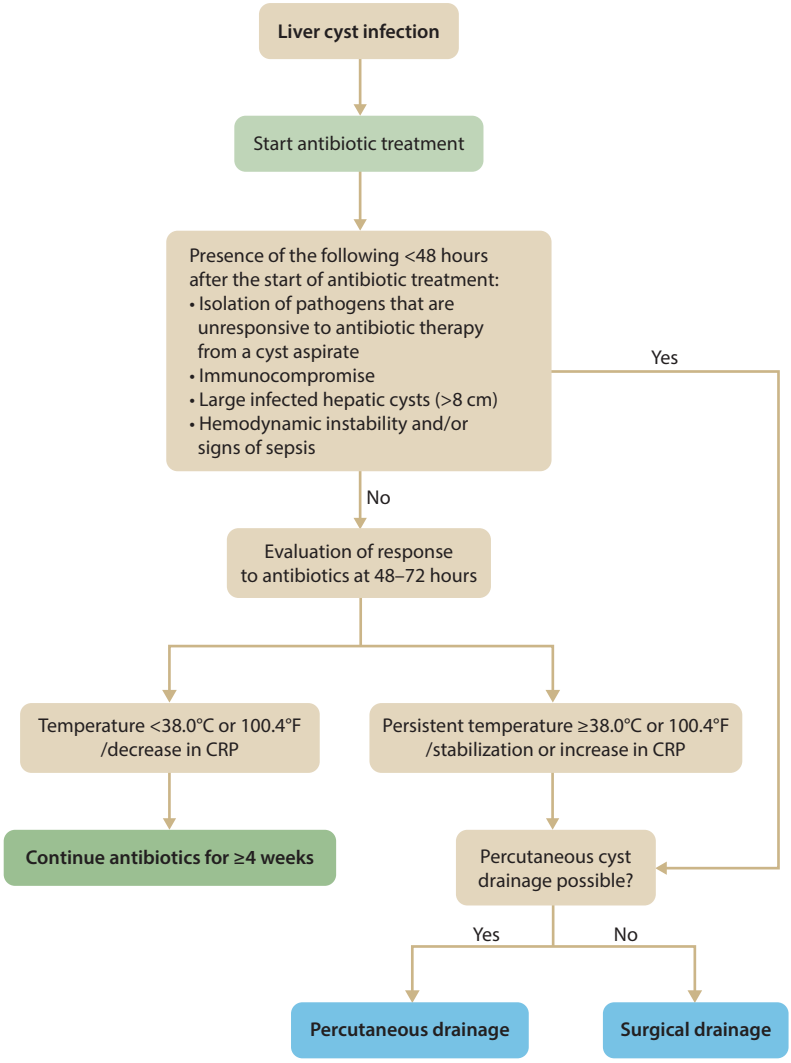


Figure 34 | Management of liver cyst infections in autosomal dominant polycystic kidney disease. CRP, C-reactive protein.

teams, so that antibiotic and immunosuppression drug levels can be adjusted as needed.

Practice Point 5.3.2.4: Percutaneous drainage of infected liver cysts <48 hours after initiation of antibiotics may be reasonable in the presence of the following:

- **isolation of pathogens that are unresponsive to antibiotic therapy from a cyst aspirate;**
- **immunocompromise in the patient;**
- **large infected hepatic cysts (>8 cm); or**
- **hemodynamic instability and/or signs of sepsis.**

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.

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

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 factors. First, penetrance of the antibiotic into the liver cyst may be limited.[564–566] 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.[563,568,571] If percutaneous drainage is not feasible, surgical drainage or partial liver resection may be used as alternative approaches.[567,568]

Research recommendations

- Studies are needed to determine the 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 and other extrarenal manifestations

6.1 Intracranial aneurysms

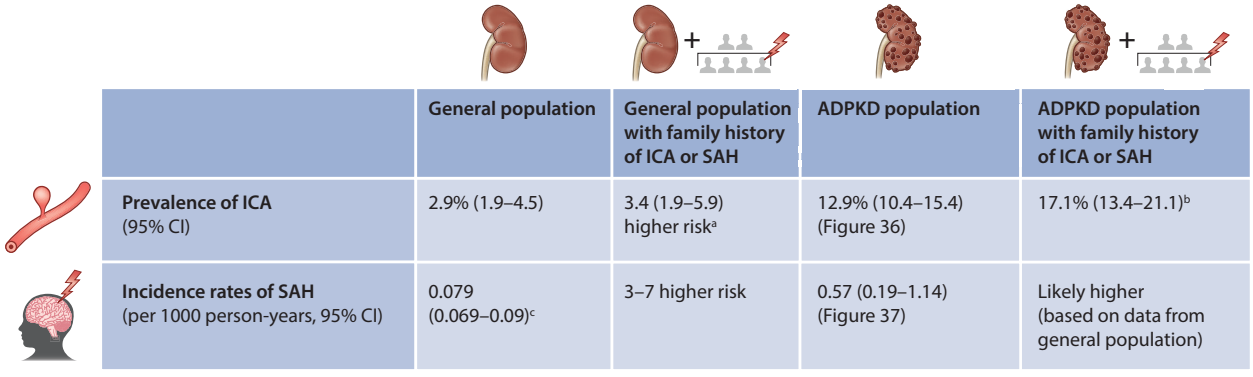
Recommendation 6.1.1: We recommend informing adults with ADPKD about the increased risk for intracranial aneurysms (ICAs) and subarachnoid hemorrhage (SAH; Figure 35) (*1C*).

ICAs are acquired, pathologic dilations at major branching brain arteries, which can remain stable, can grow with or without subsequent rupture causing SAH, or can rupture without prior growth. This recommendation places a high value on the importance of the person knowing 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 and/or personal choices that may be caused by knowing this information. The grade of certainty of evidence for this recommendation is low, because of limitations to the evidence. However, the Work Group judged that most informed people with ADPKD would wish to be informed of their risks, due to the potential catastrophic nature of the consequences.

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 ICA. Information about ICA also is essential to open the discussion, allowing healthcare providers 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 the main concerns of people with ADPKD.[581] The benefits of this information substantially outweigh the potential harms to the patients, such as anxiety associated with this information.

Unruptured ICAs are found in ~3.2% of the general population (mean age at screening, 50 years) worldwide.[578] ADPKD is associated with a 6.9-fold increased risk for developing an ICA.[578] However, the exact prevalence of unruptured ICAs in ADPKD is difficult to evaluate, because their identification depends on the selection of people to undergo imaging. Studies in ADPKD cohorts yielded prevalence estimates ranging from 9.2% to 18.5% (Figure 36).[573–577,582] Factors accounting for this heterogeneity include referral bias (i.e., some studies include primarily people 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.[575,576,583]



	General population	General population with family history of ICA or SAH	ADPKD population	ADPKD population with family history of ICA or SAH
Prevalence of ICA (95% CI)	2.9% (1.9–4.5)	3.4 (1.9–5.9) higher risk[a]	12.9% (10.4–15.4) (Figure 36)	17.1% (13.4–21.1)[b]
Incidence rates of SAH (per 1000 person-years, 95% CI)	0.079 (0.069–0.09)[c]	3–7 higher risk	0.57 (0.19–1.14) (Figure 37)	Likely higher (based on data from general population)

Figure 35 | Prevalence of unruptured intracranial aneurysms (ICAs) and incidence of subarachnoid hemorrhage (SAH) in the general and autosomal dominant polycystic kidney disease (ADPKD) populations, overall and in the presence of a family history of ICA or SAH. CI, confidence interval. [a]Prevalence ratio compared with no family history, age- and sex-adjusted. [b]Based on Evidence Review Team meta-analysis of 7 studies.[430,572–577] [c]Overall crude SAH incidence across midyear period. References: Top row, from left to right: Box 1 and 2: Vlak *et al.*[578]; Box 3: see Figure 36. Box 4: Sanchis *et al.*[576] and Xu *et al.*[577] Bottom row, from left to right: Box 5 and 6: Etminan *et al.*[579] and Rinkel and Ruigrok.[580] Box 7: see Figure 37.

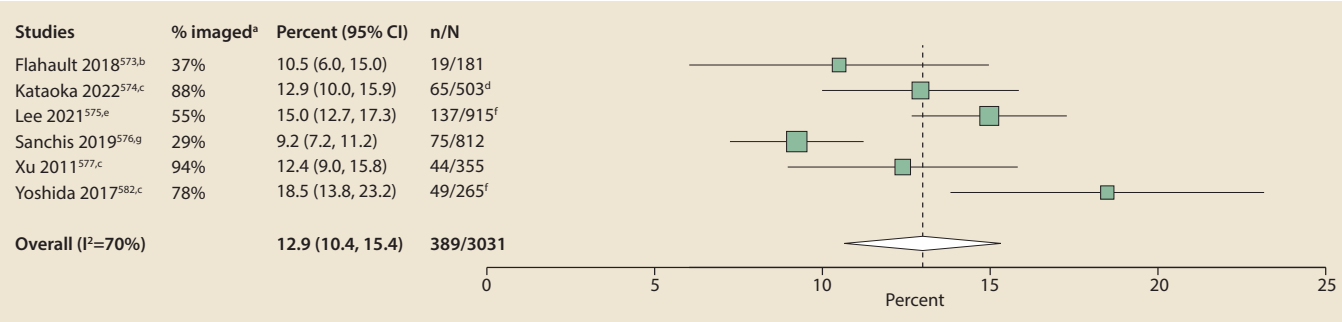


Figure 36 | Percentage of people with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) with intracranial aneurysms (ICAs) at the time of presymptomatic screening.[573–577,582] CI, confidence interval; n/N, number of cases/total number of people. [a]Percentage of all people with ADPKD (without history of known ICA) who had imaging conducted. [b]People with family history of ICA preferentially imaged (90% of such people, 21% of which with no family history of ICA). [c]Screening of all people with ADPKD who agreed. [d]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). [e]No reason reported for why imaging was conducted and number of people with known family history of ICA was not reported. [f]People with known ICA (prior to imaging) excluded from this analysis (in contrast with numbers analyzed in article). [g]No reason reported for why imaging was conducted.

Approximately 15%–25% of people with ADPKD who have an ICA have multiple ICAs.[576,583]

ICA rupture leading to SAH is associated with significant morbidity and mortality, and because ICAs are more common in ADPKD, rupture occurs more frequently in people affected by ADPKD than in the general population.[572,584–586] Although the absolute aneurysm rupture rate in the ADPKD cohort is low—0.57 per 1000 patient-years (95% CI: 0.19–1.14; Figure 37), this rate is approximately 7 times higher than that in the general population.[576,579] The median age at aneurysm rupture is ∼41 years in people affected by ADPKD, versus 52 years in the general population.[579,583]

Certainty of evidence. The certainty of evidence for estimates of both the prevalence of ICA and the incidence of ICA rupture in people with ADPKD was graded as low, due to both serious methodological limitations of the studies and inconsistency in estimates across studies (Supplementary Table S22[573–577,582,584,587,588]). In most studies, the reasons or criteria for screening were unclear, or were variable among participants. The methods for diagnosing ICA and ICA rupture were highly variable across studies.

The certainty of evidence comparing the risk of ICA rupture in people with ADPKD versus that in the general population was graded as moderate, due to serious methodological limitations of the studies (Supplementary Table S23[315,572,584,585]). Although inconsistency (statistical heterogeneity) was present in the magnitude of the ORs comparing the population with ADPKD to the 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.

Studies	Country (years)	Imaging[a], %	n/N	F/up, yr	Pt-Yr	Rate (95% CI), per 1000 pt-yr	Population[b]
Flahault 2018[573]	France (2008–15)	37	5/495	5.9	2921	1.71 (0.56, 3.99)	All patients
		37	2/181	5.9[c]	1068	1.87 (0.23, 6.75)	Imaging
Jiang 2013[587]	China (2007–08)	94	0/355	3.6	1278	0 (0, 2.88)	Imaging
Kataoka 2022[574]	Japan (2003–19)	89	3/503	6.0	3008	1.00 (0.21, 2.91)	Imaging
Sanchis 2019[576]	US (1989–2017)	27	2/812	6.7	5451	0.37 (0.04, 1.32)	Imaging
Wilkinson 2019[585]	US (2004–14)	NR	6/9110	2.8	25,408	0.24 (0.09, 0.51)	All patients
All patients or imaging[d] (I²=57%)			**16/11,275**		**38,066**	**0.57 (0.19, 1.14)**	
All patients (only) (I²=NA)			**11/9605**		**28,329**	**0.72 (<0.01, 2.73)**	
Imaging (only) (I²=5%)			**4/1851**		**10,805**	**0.64 (0.24, 1.23)**	

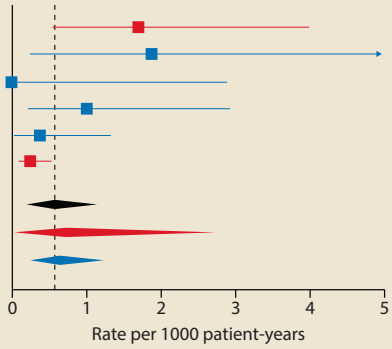


Figure 37 | Incidence rate of people with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) with ruptured intracranial aneurysms (ICAs).[573,574,576,585,587] CI, confidence interval; F/up, follow-up; n/N, number of cases/total number of people; NA, not applicable; NR, not reported; Pt-Yr, patient-years. [a]Percentage of all people with ADPKD (without history of known ICA) who had imaging conducted. [b]All patients refers to analyses of all patients without prior history of known ICA, regardless of whether they had imaging conducted; imaging refers to analyses among only those patients who received imaging prior to their ruptured ICA. [c]The follow-up period for those who received imaging was not reported, but it is assumed to be similar to that in the overall sample. [d]The analysis for all patients from Flahault *et al.*[573] 2018 is included here.

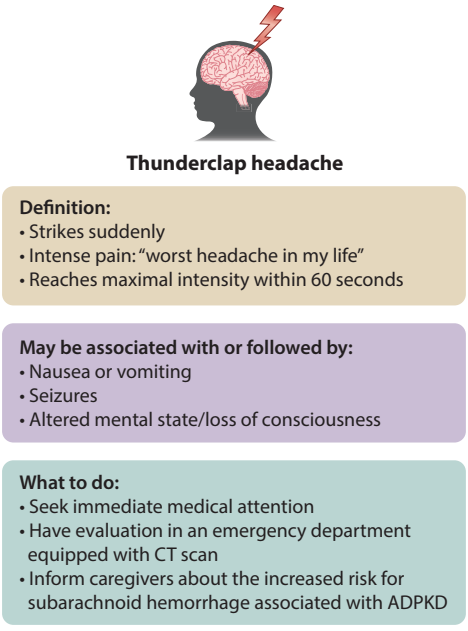


Figure 38 | Specific presentation of thunderclap headache and suggested actions. ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography.

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 to be very important, as it allows for discussion about risk factors, screening, preventive measures (lifestyle), and symptoms that should trigger immediate medical attention. The Work Group also judged that an important point to emphasize is that although ICAs occur more frequently in people with ADPKD compared with the general population, the vast majority of ICAs detected by screening will not rupture.

Resource use and costs. Informing people with ADPKD about their increased risk of ICA or SAH is important. An anticipated result is that some people will want to be screened even if they are at low risk.

Consideration for implementation. Figure 35 outlines the prevalence of unruptured ICA, and the incidence of SAH, 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. An important point to explain is that, although ICAs are found more frequently in people with ADPKD than in the general population, a large majority of the ICAs 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. Although 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 they may not inform their healthcare providers about familial history of ICA, SAH, or sudden death, or recognize thunderclap headache. A survey among 420 nephrologists from France, Belgium, and Switzerland found that when the nephrologists considered that screening was not indicated, only 35% would still systematically inform people about the risk of ICA and SAH, 53% would give information on a case-by-case basis, and 12% would not give information at all.[589]

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

Thunderclap headache or sentinel headache refers to a severe headache that has a 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 who are at higher risk for ICA.

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

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

Nonmodifiable and modifiable risk factors of ICA development and rupture are listed in Table 15. 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 the severity of the polycystic kidney disease. As observed in the population without ADPKD, women have a higher risk for ICA and SAH, especially after age 50 years.[578,590] In people with ADPKD and a positive family history of SAH or ICA, the risk for ICA is 4 times higher than it is in those with no such familial history.[430] Some studies have suggested that an association exists between the severity of ADPKD (reflected by TKV, MIC subclasses 1D–1E, and the severity of CKD G3–G5) and ICA formation.[574,582]

No genetic determinants of ICA formation and development have been identified in ADPKD. People with *PKD1* pathogenic variants appear to have a higher risk of diagnosis of ICA and SAH than do people with *PKD2*.[590] However, the role

Table 15 | Risk factors for ICAs or SAH

Evidence	Predictors for prevalent ICA or rupture of ICA and strength of the association
Evidence for association with ICA/SAH in ADPKD population	• Family history of SAH or ICA (stronger when first-degree relative)—*Strong* • Personal history of SAH or ICA—*Strong* • Tobacco smoking (especially >20 pack-years)—*Strong* • Female sex—*Moderate* • *PKD1* genotype—*Moderate* • Uncontrolled hypertension—*Moderate* • Early-onset hypertension (age <35 yr)—*Moderate* • Severity of ADPKD—*Weak*
Evidence in non-ADPKD population	• Japanese or Finnish ancestry • Alcohol in large quantity (risk factor for ICA rupture)

ADPKD, autosomal dominant polycystic kidney disease; ICA, intracranial aneurysms; SAH, subarachnoid hemorrhage.

of confounding factors cannot be excluded. First, early ICA rupture, before the diagnosis of ADPKD, might occur in some *PKD2* pathogenic-variant carriers; second, screening for ICA might be conducted more frequently in *PKD1* pathogenic-variant carriers, who generally have more severe kidney disease, resulting in closer medical follow-up. No specific *PKD1* pathogenic variant has been associated with an increased risk for ICA.[590] Earlier studies suggested an association of ICA with a 2–base-pair deletion in *PKD1* (c.5014_5015delAG), but more systematic genetic testing now has established that this variant is in fact the most common pathogenic variant of *PKD1* (∼1%–2%).[591] Although an earlier study suggested that an association exists between *PKD1* variant position and ICA, neither pathogenic variant location nor variant type were found to be associated with diagnosis of ICA or SAH in a larger and more recent study.[590,592]

Modifiable factors of ICA development and ICA rupture include tobacco smoking and hypertension.[576,577,590] In a cross-sectional study conducted in the Genkyst cohort, including about 2500 people with ADPKD, past or active smoking of over 20 pack-years and hypertension were both independently associated with a 2-fold increased risk of ICA and SAH, after multivariate adjustment.[590] In a study conducted in the Mayo Clinic cohort, hypertension and smoking history occurred significantly more frequently in people with ADPKD and ICAs than in people with ADPKD without ICAs (43% vs. 23% and 90% vs. 77%, respectively).[576,590] 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 difference also may contribute to differences in the prevalence of ICA and the 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.[593]

In the general population, the 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.[579,580] In Finland, the incidence of SAH decreased 24% from 11.7 in 1998–2000 to 8.9 per 100,000 persons in 2010–2012, corresponding with daily smoking decreasing 30% between 1998 and 2012.[594] Whether a similar decline has been observed in people with ADPKD is not known. However, 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.[595,596] The general populations in Japan and Finland have been reported to have a higher risk of ICA and SAH than do other populations.[597–599] Whether this higher prevalence also applies to people with ADPKD is currently unknown. However, 2 single-center studies in Japan reported prevalences of ICA of 17.6% and 20.1%, which are higher than those in other ADPKD cohorts.[582,600] Whether other national or ethnic 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 conducted 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.[601] 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, in predicting ICA rupture.[602] 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, evaluating the 5-year rupture risk.[597] The use of the PHASES score has not been tested in people with ADPKD, so its accuracy is unknown in this population.

Practice Point 6.1.5: People with ADPKD should be informed of the implications of ICA screening, as highlighted in Table 16.

Comprehensive information should be given by the healthcare provider prescribing cerebral imaging before a test is ordered. Adequate time should be given to the person with ADPKD to make informed decisions.

Table 16| Advantages and limitations of screening for ICAs

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

ICA, intracranial aneurysm.

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

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

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

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

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

Recommendation 6.1.2 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 16, as well as the potential harms of procedures when an ICA is found or of the anxiety of knowing about an ICA. The certainty of evidence for this recommendation is graded as very low because of its sparseness, and applicability issues in the evidence base. However, the Work Group judged that most informed people with ADPKD with a personal or family history related to ICA would wish to be screened to evaluate their risks, due to the potentially catastrophic outcomes from unidentified and untreated big aneurysms.

Key information

Balance of benefits and harms. The frequency of ICA in people with ADPKD and a positive family history of SAH or ICA undergoing screening is ∼17%.[430,572–577] The probability of identifying an ICA is ∼4 times higher in this group than it is in people with ADPKD overall, and it appears to be maximal in the case of a positive family history of SAH in a first-degree relative, and in the case of ICA and/or SAH in ≥2 relatives.[430] A point that should be noted, however, is that 50%–60% of the people with ADPKD diagnosed with ICA, and ∼40% of those with ruptured ICA, do not have any familial history of ICA and/or SAH.[576,590]

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.[603–605] The outcomes of ICA rupture in people with ADPKD do not differ from those in people without ADPKD with aneurysmal SAH.[606] At 12 months, 75% and 71%, respectively, of the people with versus without ADPKD with ICA ruptures who were 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 for adequate intervention if an ICA at risk of rupture is identified, preventing significant morbidity and/or death. In people at high risk, a negative screening can be reassuring.

The incidence of ruptured ICA from a meta-analysis of 5 population studies is presented in Figure 39. Among people with ICA found on imaging, and subsequent imaging surveillance, the incidence rate of aneurysmal SAH was 1.21 per 1000 patient-years (95% CI: 0.03–6.72; Figure 39). In people with no ICA found on imaging, the incidence rate was significantly lower, at 0.39 per 1000 patient-years (95% CI: 0.10–0.89). In 2 studies that provided follow-up information on people with ADPKD who received preventive treatment

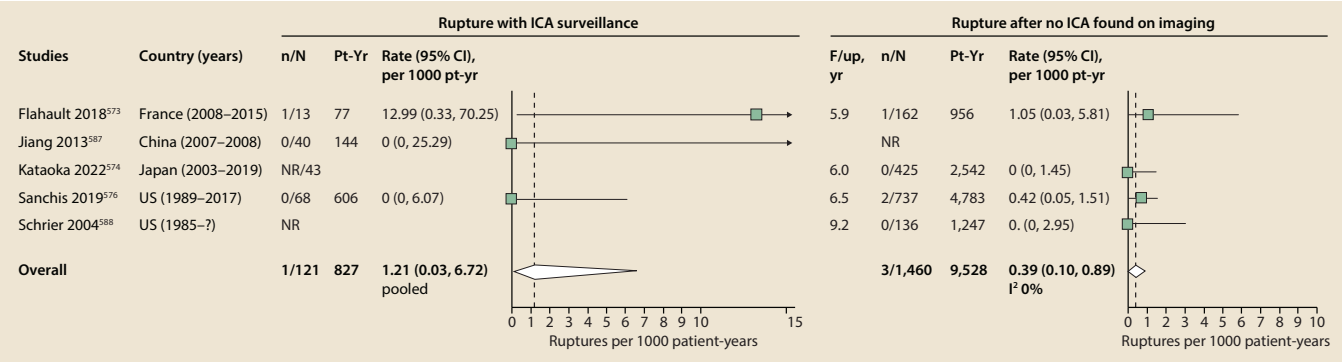


Figure 39 | Incidence rate of ruptured intracranial aneurysm (ICA) in people with autosomal dominant polycystic kidney disease with a diagnosis of ICA under imaging surveillance and in people with autosomal dominant polycystic kidney disease in whom no ICA was detected on imaging.[573,574,576,587,588] CI, confidence interval; F/up, follow-up; n/N, number of cases/total number of people; NR, not reported; Pt-Yr, patient-years.

for an ICA detected through screening, no cases of rupture were reported.[573,576]

Possible limitations of screening for ICA are listed in Table 16. These include treatment failure, the risk of complications in case of preventive treatment of an ICA (i.e., periprocedural 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 risk of complication 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 was 0.1% (95% CI: 0.0%–0.2%; 54 studies).[607] Another risk is that of finding an ICA that is too small to be treated and must receive follow-up for possible growth, a situation that may cause anxiety, affect QoL, and may limit access to life insurance, loans, and a driver's license. Despite these limitations, which should be discussed with the patient prior to prescription of imaging, this Work Group felt that the advantages of screening in people at high risk outweigh the disadvantages.

Certainty of evidence. The grade of certainty of evidence is very low regarding benefits and harms of ICA imaging (vs. not imaging) in people with an increased risk of ICA rupture (Supplementary Table S24[573,576,582]). One study with serious limitations provided imprecise estimates of the risk of death and ICA rupture, comparing people with a family history of ICA who had imaging to people without a known family history of ICA who did not have imaging.[573]

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, a strong consensus in the Work Group was to recommend screening in this group of people.[608] The Work Group judged that the majority of people would want to know their diagnosis with regard to ICA. When a familial history is not available, when ADPKD occurs *de novo,* or when the cause of sudden death is unclear in a relative affected by ADPKD, suggestions for screening appear appropriate, as familial risk for ICA cannot be evaluated precisely. The Work Group judged that an important point to mention is that screening for ICA should be performed in only those people who have a reasonable life expectancy and are eligible for treatment in case of the 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 no screening.[573,609] 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 and/or SAH is deemed to be cost effective, compared with no screening.

Consideration for implementation. ICA rupture is an exceedingly rare phenomenon in children; therefore, starting screening before adulthood is not indicated.[460] 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.[460,610] Individual candidates for screening should be informed that if an ICA is identified on screening, their relatives affected with ADPKD (particularly first-degree relatives aged >18 years) also may become eligible for screening. People also should be informed that incidental findings may be made, of issues other than ICA, including, notably, asymptomatic brain infarctions, meningioma, arachnoid cysts, and hypophyseal adenoma.[580]

Rationale

We make Recommendation 6.1.2 with consideration of the increased risk for ICA and SAH in people with ADPKD and a positive familial history of ICA and SAH, as well as the options available 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 an ICA become available (e.g., pharmacologic treatment), this recommendation likely will evolve toward one for more systematic 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 informed adequately about the potential implications of 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 single-center study conducted in 495 consecutive people with ADPKD in France concluded that systematic screening was cost effective, providing a gain of 0.68 quality-adjusted life-years, compared to targeted screening.[573] However, the aneurysm rupture rate in this study was 5 times higher than that in other ADPKD cohorts, potentially limiting the generalizability of the findings. Although the consensus is strong to recommend screening in people with a positive family history of SAH or ICA in a first-degree relative, screening also is discussed in other situations, 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 which 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 those in 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 people with ADPKD (25%), compared to 22 of 220 people without ADPKD (10%).[611] 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 recent decades.[607] The second study described a more frequent incidence of complications after endovascular coiling (hemorrhage or infarction, embolic infarction, and carotid artery dissection) or surgical clipping (hemorrhage, infarction) in people with ADPKD, compared to that in people without ADPKD (9.4% and 11.8% vs. 3.0% and 6.4%, respectively).[612] 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 is 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 they have received comprehensive information, and they should be given access to screening.

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

MRA and CTA appear to be able to detect aneurysms ≥5 mm; smaller aneurysms (down to 2 mm) are detected less reliably and may be seen in retrospect in comparing digital subtracted angiography. CTA can be considered as an initial diagnostic test for aneurysm detection and screening.[608] However, exposure to iodine contrast can be associated with degradation of kidney function, especially in people with eGFR<30 ml/min per 1.73 m^2, and can cause rare allergic reactions. Exposure to radiation can be a concern in people undergoing multiple evaluations. Besides, CTA may be limited by presence of an artifact from bone or metal (coils, stents, and clips), thereby reducing its usefulness in people with previously treated ICA.

Imaging aneurysms with MRA typically uses the time-of-flight method, and gadolinium-based contrast agents are not required. In the absence of contraindications (e,g, metallic foreign bodies, implants, external devices and/or accessory medical devices), MRA is a safe diagnostic method. However, some people may experience claustrophobia during the procedure.

Although digital subtracted angiography is still considered to be 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.

No head-to-head comparison has been made of performances of MRA versus CTA versus digital subtracted angiography in people with ADPKD, and the evidence considered here is derived from studies in the general population. The CTA sensitivity and specificity to detect small ICAs (3–5 mm) were estimated to be 95%–97% and 100%, respectively, whereas for an ICA <3 mm, the sensitivity was lower (84%–86%) without a loss of specificity.[613] Time-of-flight MRA has a detection sensitivity ranging from 74% to 98%.[614] ICA size again greatly affects the results; however, for small aneurysms (≤3 mm), the sensitivity of time-of-flight MRA at 3.0 Tesla (T) is >95%.

Although CTA and MRA do have similar sensitivities to detect aneurysms >3 mm,[615] the Work Group judged that the majority of people would choose MRA as the screening method of choice, as it allows limitation of the exposure to radiation and iodine-contrast, particularly in people with an eGFR <30 ml/min per 1.73 m^2. CTA also has a high diagnosis

accuracy and is a valid alternative, when MRA is not available or when contraindications to MRA are present. Digital subtracted angiography is associated with risks for complications, albeit rare, and for this reason, it should not be used routinely in the setting of presymptomatic screening.

The financial burden or limited availability of MRA in some areas may reduce access to MRA as a first-line imaging method. In the absence of a contraindication, CTA can be considered as an initial diagnostic test for screening, and it remains more accessible than MRA in several countries and areas. In cases in which results from a first imaging are equivocal, another technique occasionally may be needed (e.g., MRA with a 3.0-T magnet after 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 an MRA is prescribed for them. The presence of a contraindication for CTA (e.g., allergy to iodine, eGFR$<$30 ml/min per 1.73 m^2, pregnancy) also should be reviewed.

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

Only limited evidence is available 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 that included 76 people with ADPKD and initial negative MRA, 2 people developed an ICA on rescreening after 10 years.[616] 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, and among 734 people with initial negative MRA and clinical follow-up available, 2 people, both with positive family histories, had a ruptured aneurysm.[576] Based on this limited evidence, 5–10-year intervals generally are suggested, but this approach should be discussed and individualized according to family history of SAH, life expectancy, possibility of intervention in case of positive screen, and risk factors (i.e., number of affected relatives with ICA and/or SAH, tobacco use, uncontrolled hypertension). An important point to note is that, despite repeated screening and preventive treatment of unruptured ICAs, not all episodes of SAH can be prevented. In rare instances, ICAs 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.[573,617] The role of rescreening in people with negative imaging and without a family history is less clear and should be discussed on a case-by-case basis, after the benefits and harms of screening, highlighted in Table 16, have been discussed.

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

Only limited information is available on the natural history of ICAs in people with ADPKD and, as previously mentioned, no predictive tools are currently available 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.[430] In a follow-up study, 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. *De novo* ICAs measuring $\geq$2 mm were also detected in 5 people.[576] These studies suggest that the risk of rapid expansion or rupture of small, unruptured ICAs detected by screening in people with ADPKD is low.

Decisions regarding the management of ICA should be assessed in a multidisciplinary setting, including experienced radiologists, neurosurgeons, and neurointerventional radiologists. Key factors in making a decision to intervene and the choice of intervention are the general health and life expectancy of the affected person; the size, shape, and location of the ICA; the growth of ICA when follow-up imaging is available; the risk factors for rupture (history of SAH, smoking, and hypertension); and the estimated risk of treatment (comorbid disease, ICA morphology).[618] The recent European guideline on the management of unruptured ICA does not provide a general recommendation stating which treatment modality (endovascular vs. microsurgical) is preferred, but it does insist on the importance of therapeutic decisions and treatments being made in centers of expertise with high ICA case volumes.[618] For ICA occurring in the posterior circulation, endovascular treatment is advised as the first option to consider.[618]

In people with unruptured ICA with no indication for treatment, radiologic monitoring to detect ICA growth, morphologic modification, and/or *de novo* ICA should be continued as long as preventive treatment remains an option.[618] The frequency of MRA or CTA is individualized based on ICA- and patient-related risk factors for rupture; it usually varies from being at 6-month intervals initially to being at intervals of 1–2 years.[608]

6.2 Other vascular associations

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

Dilatation and dissection of non-intracranial large arteries (thoracic aorta, coronary, cervicocephalic, vertebral) have

been described in people with ADPKD.[619,620] 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.[621–629] Although the number of reported cases is limited, the broad range of vascular abnormalities observed in people with ADPKD, including arterial aneurysms and dissections, suggests that people with ADPKD may be at increased risk for thoracic aortic, carotid, vertebral, and coronary artery dissections.

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

Whether ADPKD is associated with an increased risk for abdominal aorta aneurysms is uncertain. A single-center study from Spain enrolling 139 people with ADPKD and 149 family members without ADPKD showed similar abdominal aortic diameters in both groups, across all age groups.[630] A population-based cohort study from Taiwan's National Health Insurance Research Database reported an ∼5-fold greater risk for aortic aneurysms and dissection occurrence in people affected by ADPKD, as compared to the risk in their counterparts without ADPKD. This increased risk appeared to be driven by an increased occurrence of thoracic aortic aneurysm (TAA), which was highest in people with ADPKD and hypertension.[631]

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.[632–635] Familial clustering of TAA in people with ADPKD also has been reported.[636,637] 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, and significantly higher Z-scores (normalized for sex, age, and body surface area) for both the sinuses of Valsalva and the thoracic ascending aorta in those with ADPKD.[304]

Although specific studies to assess the familial risk for TAA in people with 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 a diagnosis of TAA.[638,639] For this reason, screening of first-degree relatives should be considered for diagnosing TAA.

In people eligible for screening (e.g., first-degree relatives of a person with a diagnosis of TAA), a contrast-enhanced CT scan or MRA can be performed. Transthoracic echocardiography is a standard approach to identifying and monitoring 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 should be offered; these include smoking cessation, statin therapy, and antihypertensive therapy including a beta-blocker and an ACEi or ARB.

No specific studies have been done in the ADPKD population, and most trials have focused on cohorts of people with either Marfan syndrome or abdominal aortic aneurysm. Uncontrolled hypertension increases the risk for aortic dissection[640]; therefore, achieving a BP target, as detailed in Chapter 2, can reduce the incidence of adverse clinical outcomes. The most robust evidence of antihypertensive therapy in abdominal aortic aneurysm is that for beta-blockers and RASi.[640] Although mostly studied in the context of abdominal aortic aneurysm, statin therapy may provide a protective effect by targeting inflammatory and atherosclerotic pathways.[640]

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.[641–643]

6.3 Cardiac associations

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

In people with hypertension, echocardiography is the preferred method to detect left ventricular hypertrophy.[644] Valvular abnormalities, including mitral valve prolapse and aortic regurgitation, can be detected by echocardiography in people with ADPKD.[305,645] Mitral valve prolapse formerly was reported to be present in 20%–30% of the people with ADPKD, but more recent studies using the current definition of MVP reported a prevalence of 1% in pediatric and 3.4% in adult cohorts, similar to those in the general population.[646,647] Most people with valvular disease are asymptomatic, and some may 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 those in the general population.[648,649] However, the rarity of these cardiomyopathies, and the limited evidence for this association, does not support systematic screening in all people with ADPKD. In case of a positive familial history of nonischemic cardiomyopathy, presymptomatic echocardiography should be performed. Lastly, because familial clustering of TAA has been reported, presymptomatic echocardiography should be performed in people with a familial history of TAA.

6.4 Abdominal wall hernia

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

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

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

Although published evidence in the literature is limited describing an increased risk for abdominal wall hernias in people with ADPKD, a strong consensus in the Work Group was to designate abdominal wall hernias as a common clinical situation in ADPKD. The published evidence included mostly people with ADPKD and kidney failure, who are more likely to have enlarged kidneys (and/or an enlarged liver). One study reported a 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%); the difference was reported to be significant for inguinal, incisional, and paraumbilical hernias.[650] A point of interest is that 18 people were diagnosed before the detection of abnormal kidney function, suggesting that nephromegaly is not the only driver of the development of hernia.[651] Another study describes a higher incidence of inguinal hernia in people with ADPKD receiving PD, compared to that in people without ADPKD undergoing PD.[652] A meta-analysis showed that the risks of abdominal hernia were higher in people with ADPKD undergoing PD than they are in other etiologies of kidney failure (see Chapter 3).[653] 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 cyst infection, and recurrence of hernia. Thus, for people with severely enlarged kidneys and/or liver, an advisable approach is to monitor abdominal wall hernias whenever feasible, and people should receive education to promptly recognize signs of acute complications, 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 evaluated carefully before surgical repair is performed (see Chapter 3).

Indications for surgical treatments vary also according to the site of hernias. Femoral hernias are associated with a higher risk of developing complications than are inguinal hernias, and hence surgical repair, rather than watchful waiting, is usually suggested. People also should be counseled about modifying risk factors, including via smoking cessation, medical optimization (e.g., diabetes), and weight loss when indicated.

6.5 Other extrarenal manifestations

Table 17 outlines some of the central nervous system, cardiovascular, hepatic, gastrointestinal, and other extrarenal manifestations of ADPKD. Table 17 also provides the

Table 17 | Extrarenal manifestations

Extrarenal manifestations described in ADPKD	Estimation of the % of people affected by ADPKD	Details or notes	Guidance for imaging
Central nervous system manifestations			
Intracranial aneurysm	Summary: 12.9% (95% CI: 10.4%–15.4%)	Prevalence in ADPKD population is difficult to assess because systematic screening is usually not performed.	See Recommendation 6.1.2 and Practice Point 6.1.6.
Subarachnoid hemorrhage	Summary: Incidence rate 0.57 per 1000 patients/yr (95% CI: 0.19–1.14)	Thunderclap headache should lead to immediate medical attention.	Only if symptoms are present
Intracranial arterial dolichoectasia	~0.7%–5%[654]	Dolichoectasia (dilatative arteriopathy) is usually asymptomatic, but may cause stroke, and may mimic ICA on imaging studies.	No systematic screening
Arachnoid cyst	8%–15%[655–659]	Usually asymptomatic, incidental diagnosis Possible increased risk of spontaneous subdural hematoma	No systematic screening
Meningeal cyst	Rare case reports[660,661]	Usually asymptomatic, incidental diagnosis May very rarely cause spontaneous intracranial hypotension	No systematic screening
Cardiovascular manifestations			
Mitral valve prolapse and regurgitation	MVP 3%–26%[305,306]	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 in the general population.	No systematic screening

(*Continued on following page*)

Table 17 | (Continued) **Extrarenal manifestations**

Extrarenal manifestations described in ADPKD	Estimation of the % of people affected by ADPKD	Details or notes	Guidance for imaging
Pericardial effusion	~20%[662]	Usually asymptomatic, incidental diagnosis	No systematic screening
Cardiomyopathy	Rare[648]	Hypertrophic cardiomyopathy: 2.5%[a] Dilated cardiomyopathy: 5.8%[a] Left ventricular noncompaction: 0.3%	No systematic screening[302,663,664]
Congenital heart malformation	Very rare[648]	Very rare case-series and case reports Left-to-right shunt, obstructive cardiomyopathies (aortic coarctation, congenital pulmonic stenosis) and other complex malformations have been reported.	No systematic screening
Situs inversus and large vessels transposition	Rare case reports[665–667]	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).	No systematic screening
Thoracic aortic aneurysm	~1.5%[620,631]	See Practice Point 6.2.2.	No systematic screening. To be considered in case of positive familial history
Thoracic aortic dissection	Very rare case reports[632,637,640]	Acute chest/upper back/abdominal pain is present in >90% of the cases.	Only if symptoms are present
Coronary artery dissection	Very rare case reports[629]	People generally present with symptoms and signs characteristic of acute myocardial infarction. Usually more frequent in young women	Only if symptoms are present
Carotid and vertebral artery dissection	Very rare case reports[625]	Often result in ischemic stroke or transient ischemic attack, often associated with neck pain or headaches Occasional Horner syndrome in case of carotid dissections	Only if symptoms are present
Retinal artery and vein occlusion	Very rare[668]	Single case-series of 8 people with ADPKD	No systematic screening
Hepatic and gastrointestinal manifestations			
Symptomatic polycystic liver disease	<5% predominant in females	Liver cysts are present in >80% by age 30 yr.	Include liver imaging in initial visit (Chapter 5)
Congenital hepatic fibrosis	Very rare case reports[669,670]	More common in ARPKD	No systematic screening
Pancreatic cysts and IPMN	Pancreatic cysts ~10%[671]	Any complex pancreatic cyst or in case of multiple cysts should be followed and evaluated to exclude malignancy.	No systematic screening
Splenic cysts	~7%[672]	Like general population Usually asymptomatic, incidental diagnosis	No systematic screening
Abdominal wall hernia	Common[650]	Published evidence from a small cohort in Wales but very common clinical finding	Clinical examination
Dilated extrahepatic bile duct	~40%[673]	Small-cohort single study	No systematic screening
Colonic diverticulosis	1.5% of all people with ADPKD (vs. 0.8% of general population; adjusted OR: 1.88; 95% CI: 1.82–1.93)[317] 2.6% of people with kidney transplant and ADPKD (vs. 0.8% of people with kidney transplant without ADPKD)	Single, large national database	No systematic screening
Duodenal or small-bowel diverticula	Rare case reports[674]	Rarely, periampullary duodenal diverticula may be associated with obstructive jaundice or ascending cholangitis. Small-bowel diverticula may be associated with bacterial overgrowth.	No systematic screening
Other manifestations			
Bronchiectasis	19%–37%[675,676]	Incidental radiology finding typically of no clinical significance	No systematic screening
Pleural effusion	21% vs. 8% in controls[677]	Incidental radiologic finding, more frequent in females, not clinically significant	No systematic screening

Table 17 | (Continued)

Extrarenal manifestations described in ADPKD	Estimation of the % of people affected by ADPKD	Details or notes	Guidance for imaging
Sperm abnormality	Abnormal semen parameters reported[678]	May be associated with male infertility, although no large study has demonstrated that male infertility was more common in ADPKD.	No systematic screening
Seminal vesicle cysts	20%–40%[678,679]	Although commonly identified, seminal vesicle cysts do not result in male infertility.	No systematic screening
Seminal vesicle ectasia	Ectasia >10 mm: 23%[680]	Although commonly identified, seminal vesicle ectasia does not result in male infertility.	No systematic screening
Thyroid cysts	Case reports[681,682]	Very limited number of cases Uncertainty about specific link with ADPKD A small case-series suggests no increased prevalence in people with ADPKD.	No systematic screening

ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CI, confidence interval; CKD, chronic kidney disease; ICA, intracranial aneurysm; IPMN, intraductal papillary mucinous neoplasms; MVP, mitral valve prolapse; OR, odds ratio.
[a]Estimates taken from a single study and should be considered with caution.

proportion of people with ADPKD for each category, and guidance for screening.

Research recommendations

- Studies are needed to better evaluate the frequency of ICA and SAH in people affected by ADPKD, including according to their geographic ancestry.
- Research is needed to provide a better definition of the appropriate interval between screenings for unruptured ICA or in the case of a negative screening result.
- Studies are needed to identify the risk factors for ICA rupture. Validation is needed of predictive tools, such as the PHASES 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 whether people with ADPKD and more severe kidney involvement (i.e., MIC subclass 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, and uncontrolled hypertension, to further distinguish between people at low risk versus at high risk with ADPKD.
- Studies are needed to identify the genetic factors (e.g., genetic variants coinherited with a *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 effects 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, healthcare providers need to provide patients with advice and guidance regarding nutrition, lifestyle, physical activity, and management of psychosocial issues (Figure 40). Care can be provided by the core multidisciplinary care team or by referral to dedicated services.

7.1 Nutrition intake

ADPKD is a lifelong condition, associated with complications (e.g., hypertension, CVD, kidney failure, kidney stones) that can be affected by dietary measures (Chapters 2 and 3). No large dietary intervention trials in people with ADPKD suggest that nutrition in people with ADPKD should be different than for other people with CKD. In the absence of large dietary trials in populations with ADPKD, maintenance of good general physical health and prevention of premature CVD are important. A healthy diet and lifestyle regimen has to be established early and maintained over the long-term, with the support of accredited and/or 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 (Table 18).

People with ADPKD should consume a well-balanced diet with high intake of vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts, and low intake of processed meats, refined carbohydrates, and sugar-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; hence, its applicability to people with ADPKD is reasonable (Figure 40).[690–692,694,695]

An important point to note is that the guidance in Table 18 may be based on dietary patterns observed in Western countries. Healthcare providers should tailor their dietary recommendations to the specific regional and individual needs of their patients, based on national dietary guidelines.

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

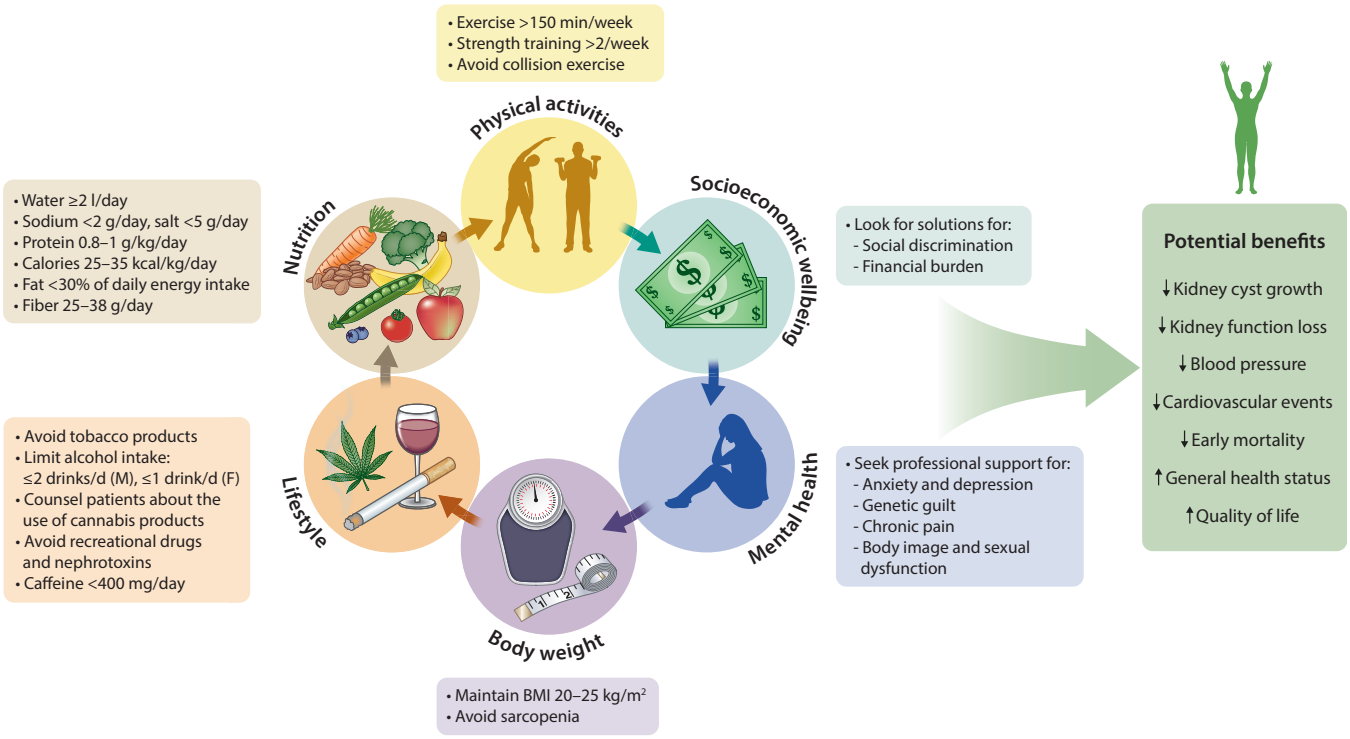


Figure 40 | Lifestyle and psychosocial care for improved outcomes in people with autosomal dominant polycystic kidney disease (ADPKD). BMI, body mass index; F, female; M, male.

Table 18 | Nutrition guidance for people with ADPKD and CKD G1–G4

	Recommended daily intake	Comments and impact on ADPKD
Water	≥2 l/d Maintain morning urine osmolality <280 mOsm/kg[a]	• High water intake prevents kidney stones and may reduce kidney function loss.[485] • May need to adjust daily intake depending on concomitant medications and capacity to dilute the urine to minimize the risk of hyponatremia • Refer to Chapter 4 for more details.
Salt	Sodium <2 g/d (equivalent to <90 mmol sodium/d or <5 g salt/d)	• Recommended by WHO for the general population[683] • High salt intake in the observational CRISP study and in *post hoc* analyses of clinical trials in people with ADPKD has been associated with faster increase in kidney volume and, at later stages (eGFR 25–60 ml/min per 1.73 m^2), with faster decline in kidney function.[141,142,684] • People with ADPKD should be counseled against adding salt to their food, and to avoid processed foods (typically high in sodium) as much as possible.
Protein	0.8–1 g/kg (weight)/d	• Recommended by WHO for the general population[485,683] • No benefit of protein restriction has been demonstrated; however, excess dietary protein (≥1.3 g/kg/d) may be harmful.[485] • Plant-based proteins are preferred to animal proteins from red and processed meat.[685]
Calories	25–35 kcal/kg/d	• High BMI and obesity are associated with many adverse health conditions and may be associated with accelerated ADPKD progression.[140,683,686] • Individualized to prevent or treat overweight and obesity
Fat	<30% of daily energy intake (70 g/d [F], 87 g/d [M])	• Recommended for the general population[687,688] • Saturated fat limited to <10% of total fat
Fiber	25–38 g/d (14 g per 1000 calories)	• Recommended for the general population[689–691]
General	A well-balanced diet[690] High in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts Low in processed meats, refined sugar, and sugar-sweetened beverages	• Recommended by WHO for the general population[692] • At least 400 g (5 portions/d) of fruit and vegetables, excluding high-starch foods such as potatoes[692] • Minimize the intake of added sugars and sugar-sweetened beverages, aiming to limit free sugars to <10% of total energy intake, and ideally to 5%.[692]
Stone prevention		• Specific dietary assessment and recommendations for the prevention of kidney stones (Recommendation 2.3.3)[693]

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CKD, chronic kidney disease; CRISP, Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease; eGFR, estimated glomerular filtration rate; F, female; M, male; TKV, total kidney volume; WHO, World Health Organization.
[a]Using second morning urine sample.

People with ADPKD and CKD G4–G5 should continue healthy eating practices, but they may need individualized dietary counseling to prevent the classical metabolic complications of advanced CKD, including hyperkalemia, metabolic acidosis, and bone and mineral abnormalities. Currently, no studies suggest that people with ADPKD and CKD G4–G5 should be treated differently from people with CKD from other etiologies.[696] Prevention and treatment of hyperkalemia, metabolic acidosis, and mineral abnormalities are discussed in the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*.[237] Hyponatremia may develop if people with ADPKD continue a high water intake at CKD G4–G5, particularly if they are also treated with other medications that predispose them to hyponatremia (e.g., selective serotonin reuptake inhibitor [SSRI]). Water intake has to be individualized in these people.

Preclinical trials have indicated that a ketogenic diet has the potential to decrease cyst burden and prevent kidney-function loss. The efficacy and safety of ketogenic interventions (through diets that induce ketosis and/or treatment with ketone supplements) have not been established in people with ADPKD, and are not recommended in the absence of further evidence.[489,490]

Practice Point 7.1.3: People with ADPKD who either have or have an increased risk of developing urinary stones should make dietary adjustments to prevent stone formation. The dietary strategy will depend on the composition of the stones or the concentration of lithogenic molecules in the urine.[693,697]

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

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

A healthy (adjusted) BMI of 20–25 kg/m^2 (after excluding the excess weight of severely enlarged kidneys and/or liver; see Practice Point 3.2.7 and Figure 20) 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.[349,698–701]

Healthcare providers also should inform patients that obesity itself can cause kidney disease, notably the glomerular disease focal segmental glomerulosclerosis (FSGS), 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.[699,702–710] Furthermore, *post hoc* analyses of the HALT-PKD and the TEMPO 3:4 trials also suggest that overweight and obesity are associated with more rapid progression of ADPKD.[140,686,711]

The impact of a 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.[483]

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

A more accurate assessment of weight and BMI is derived from subtracting the patient's total kidney and liver weights (calculated from the imaging estimated volumes) from the patient's total body weight. Long-term calorie restriction is unnecessary for people who are not overweight or obese. 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.[699,709] As an additional benefit, in the HALT-PKD trial, weight loss of ≥4% per year also was associated with favorable effects on pain in people with ADPKD.[712] However, currently, no evidence is available to recommend any specific type of diet to lose weight in ADPKD. In animal studies of ADPKD, caloric restriction reduced the incidence of the cystic kidney phenotype.[136,137,713] In ADPKD, daily caloric restriction, rather than intermittent fasting, has shown more promise for inducing weight loss, according to a pilot study.[713] Therefore, a "balanced, low-calorie diet" based on healthy foods is advised for people who are overweight or obese with ADPKD, as current evidence does not support any particular diet for achieving sustained weight loss.

Some people may be more motivated to lose weight when they are told that doing so is necessary to receive a kidney transplant. However, attempting weight loss at later CKD severities (CKD G4–G5) is controversial and is perceived to not always be safe, because of an increased risk of hyperkalemia, metabolic acidosis, and malnutrition.[714,715] Dietary interventions often fail to achieve significant weight loss, whereas bariatric surgery has been successful in selected kidney transplant candidates.[716]

Tailored dietary interventions and other weight-control strategies, including medication and exercise, which are essential for people with ADPKD, especially those with CKD G4–G5, should be supervised by healthcare providers, ideally within a multidisciplinary obesity-management team. Such interventions should be personalized, considering the different cultural, age, gender, and societal perspectives on body size, weight, and obesity that come into play in patient care.[715]

Only limited research has been done on pharmacologic agents for obesity in people with ADPKD. The GLP-1 RAs (e.g., semaglutide, tirzepatide, liraglutide, dulaglutide) are prescribed frequently for obesity, given their relative safety in people with CKD, and their effectiveness in reducing the risk of the occurrence of major adverse cardiovascular events and composite kidney outcomes.[717] However, caution is warranted, particularly when initiating or adjusting the dose in people with kidney disease, especially in cases of advanced kidney disease (CKD G4–G5).[718]

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

In addition to abnormal kidney function, organomegaly due to massive cysts, especially in the liver, is a risk factor for malnutrition in people with ADPKD (for evaluation of sarcopenia and malnutrition, see Practice Points 5.2.2.2 and 5.2.2.3). Regular assessment of nutritional status by tools such as the Patient-Generated Subjective Global Assessment (PG-SGA) or the 7-point Subjective Global Assessment (SGA), in conjunction with bioelectrical impedance analysis (BIA), mid-arm circumference, or BMI to ensure a thorough evaluation of nutritional status and timely intervention by registered dieticians or accredited nutrition providers, are particularly important.[719]

Research recommendations

- Epidemiologic studies are needed to assess the impact of overweight (defined by adjusted BMI >25 kg/m^2, the presence of the metabolic syndrome or of visceral adiposity), dietary components (e.g., excess carbohydrate, fat, or caloric intake), and specific dietary interventions (e.g., weight loss, low intake of carbohydrates, fat, or both) on clinical and metabolic features and disease progression in people with ADPKD—taking into account regional specificities.
- Low osmolar diets could potentially reduce ADPKD progression by lowering vasopressin level, shown by decreased plasma copeptin and urine osmolality[376]; further studies are needed to evaluate their long-term viability and benefits.
- Large RCTs of longer duration are needed to determine the efficacy and safety of the keto (or ketogenic) diet and/or β-hydroxybutyrate supplementation, in relation to known risks, such as hyperlipidemia and nephrolithiasis.
- Well-designed clinical trials are needed to determine the optimal dietary and pharmacologic interventions for achieving sustained control of overweight and obesity in people with ADPKD.

7.2 Physical activity

Maintaining general health and physical fitness is particularly important for people with a lifelong disease, such as ADPKD. Physical activity may help control hypertension and improve cardiovascular health in people with ADPKD. Physical activity contributes to good QoL, counteracts depression, and helps in maintaining a healthy body weight. Physical fitness is essential for people with kidney failure, so that they maintain their status as 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 for at least 1 hour, twice per week.

The health benefits of regular physical activity are well known. Even though no specific studies have examined 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 Diabetes Management in CKD* also can be applied to people with ADPKD.[216] Briefly, clinical advice for physical activity should be determined with consideration for age, ethnic background, presence of other comorbidities, access to resources, and risk of falls (among people with sarcopenia). People with ADPKD should avoid sedentary behavior and be encouraged to undertake regular activities to improve or maintain muscle strength, balance, and flexibility, and they should break up prolonged periods of being sedentary with periods of light activity.

Most people with ADPKD can follow guidelines that recommend that adults (aged ≥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, healthcare providers should routinely assess the level of physical activity and, if necessary, prescribe structured exercise and increased lifestyle activities to all people with ADPKD.[720]

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

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.[722]

Direct trauma to the kidneys and/or liver is a particular concern for contact sports, and bleeding is more likely to occur if cysts are superficially located and are 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) and to use protective equipment, such as an athletic "corset."

For individuals, if a particular type of physical activity is consistently associated with macroscopic hematuria and/or flank pain (presumed cyst ruptures), the best approach is to avoid this activity. This suggestion is based on the belief that bleeding due to cyst ruptures leads to subclinical kidney injury, thereby accelerating the progression of ADPKD.

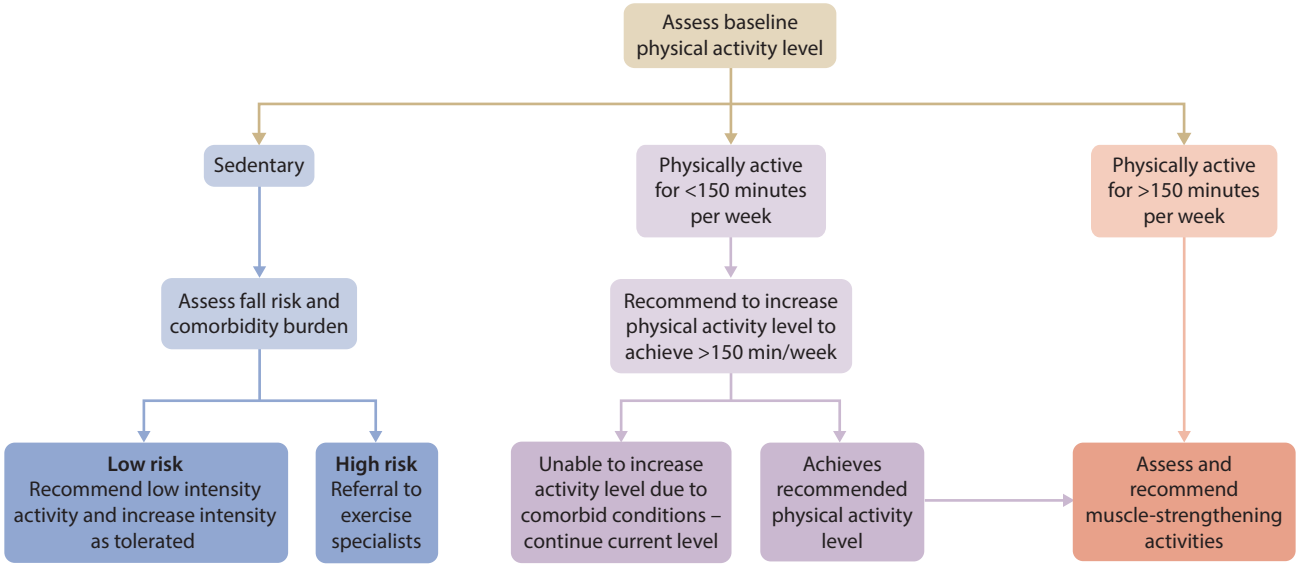


Figure 41 | Suggested approach to address physical inactivity and sedentary behavior in chronic kidney disease (CKD). The evaluation of fall-risk should ideally utilize fall risk–assessment tools used by each healthcare institution. The tool should consider factors such as history of falls, mobility, medications, cognitive status, and environmental factors.[721] Reproduced from *KDIGO Clinical Practice Guideline for Diabetes Management in CKD*.[216]

On the other hand, hematuria may occur in absence of direct trauma, after running and jumping, for example, or even gardening, presumably because of stretching or abruptly changing forces on small blood vessels in cyst walls. Hematuria episodes also can occur at rest, and most people with ADPKD exercise without resulting hematuria; therefore, in the judgment of the Work Group, given the large health benefits of regular physical activity, discouraging exercise for people with ADPKD, particularly young people, is not appropriate.

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

Many barriers to exercise come into play for people with high-risk of an adverse event. The most important barriers are fatigue and weakness, due to comorbidities or to dialysis procedures, lack of time and equipment, lack of a place to exercise, and cost of going to a gym. People with ADPKD treated with dialysis and transplantation should undertake as much physical activity as they can. People receiving dialysis frequently have a reduced aerobic and functional capacity, an elevated 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 for both cardiovascular problems and muscle atrophy in people receiving dialysis.[723]

Research recommendations

- Epidemiologic 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," decreases the incidence of episodes of cyst hemorrhage.
- Studies are needed to identify appropriate exercises for people with ADPKD, and how to best support their participation in physical activity.

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 care model and specialized clinics for genetic diseases (Table 19; Chapter 10).[724]

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 a higher incidence of cardiovascular and cerebrovascular events than do nonsmokers, a higher risk of intracranial and other aneurysmal formation and rupture, a likely accelerated progression of ADPKD, more endothelial dysfunction, and more proteinuria.[217,576,583,725,737] People should be asked about their use of tobacco products intermittently, as they may change their usage (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 if female and ≤2 drinks per day if male.

People with ADPKD who consume alcohol should follow the guidelines for alcohol consumption for the general population.[689,738] Light alcohol consumption may decrease cardiovascular risk. Moderate alcohol consumption does not appear to be associated with a 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 who consume it, and their loved ones.[738]

Although no studies suggest that people with ADPKD should stop or reduce their alcohol consumption, 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).[726] This association was confirmed in a subsequent meta-analysis that also found evidence of a linear dose-response.[727]

Healthcare providers should advise people who engage in excessive alcohol consumption, particularly young people, to reduce or stop their drinking, in collaboration with a clinic for alcohol use disorder, or its equivalent for behavioral and pharmacologic intervention. Healthcare providers should counsel people to drink more water than usual when they consume alcohol, to avoid harmful dehydration.

People should be asked intermittently about their use of alcohol, as they may change their usage (e.g., starting, stopping, or increasing intake) at any time during their lives.

7.3.3 Caffeine

Caffeine intake restriction may inhibit cyst enlargement in animal models of cystic disease, but it has not been shown to be effective among people with ADPKD.[739] In terms of cardiovascular complications, coffee consumption is not considered a long-term risk factor for heart disease, although excessive coffee consumption may lead to coronary and arrhythmic disease in susceptible people.[740] For pregnant women with a high daily caffeine intake (>300 mg/d),

Table 19 | Recommendations on use of common lifestyle products in people with ADPKD

Product	Recommendation	Supporting explanation
Tobacco products	Avoid use of all tobacco products	• Increased cardiovascular and cerebrovascular events in ADPKD[725] • Higher risk of intracranial and other aneurysmal formation and rupture in ADPKD[576,583,726] • Accelerate progression of ADPKD[440] • Can cause endothelial dysfunction and proteinuria[217]
Alcohol	≤1 alcoholic drink/d for F patients or ≤2 drinks/d for M patients	• Moderate alcohol consumption is not associated with higher risk of abnormal kidney function, increased mortality, and other medical morbidities.[689] • Excessive alcohol intake (>150 g/wk [0.15 kg/wk]) is a significant risk factor for subarachnoid hemorrhage.[726,727]
Caffeine	<400 mg/d (approximately 4 cups of coffee per 250 ml cup)	• Recommendation for general population from the U.S. Food and Drug Administration and European Food Safety Authority[728] • This is roughly equivalent to about 4 cups of brewed coffee, 10 cans of cola, or 2 "energy shot" drinks. • Administration of caffeine accelerates cyst enlargement in animal models of cystic disease, but caffeine restriction has not been shown to be effective among people with ADPKD.[129] • Lowering daily caffeine intake during pregnancy is recommended (<200 mg/d [~2, 8-oz cups of coffee]).[729,730]
Cannabis	Not recommended	• No evidence of clinical benefits of cannabis • Potential danger of AKI[731]
Cocaine and methamphetamines	Avoid	• Cause elevated BP, hypertensive crises, and vasospasm, which could increase the risk of ICA rupture[732,733] • AKI requiring dialysis that may not resolve[734]
Anabolic steroids	Avoid	• Increased risk of CKD and kidney failure[735]
Creatine supplements	Avoid for people with kidney disease	• Creatine supplementation is associated with increased serum creatinine levels.[736] • Patients with kidney disease are advised to avoid creatine supplements to prevent misinterpretation of serum creatinine levels.[736]
Others	Not recommended	• Currently, no data or insufficient human data support the use of supplements or nutrients in slowing ADPKD, such as β-hydroxybutyrate, curcumin, ginkolide B, saponins, vitamin E, niacinamide, triptolide, omega-3 fatty acids, eicosapentaenoic acid, α-lipoic acid, or isoflavones.[485]

ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; BP, blood pressure; CKD, chronic kidney disease; F, female; ICA, intracranial aneurysm; M, male; U.S., United States.

lowering their daily caffeine intake to <200 mg/d during pregnancy is recommended to reduce the risk of pregnancy loss and of having neonates with low birth weight.[729,730]

7.3.4 Cannabis products

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

People with ADPKD are at greater risk for AKI due to decreased kidney function. Case reports have been made of synthetic cannabinoids causing significant AKI.[731] Currently, no evidence has been reported, beyond anecdotal case reports, of any clinical benefits of cannabis use. An important point to note is that the toxicity of these products is not always due to the drug itself, but rather sometimes to its contaminants, the presence of which is often unknown to the user. In absence of dedicated studies, we advise against the use of cannabis products to alleviate complications in people with ADPKD.

People should be asked intermittently about their use of cannabis products, as they may change their usage (e.g., starting, stopping, or increasing intake) at any time during their lives.

7.3.5 Nephrotoxins

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

Use of cocaine and methamphetamines can cause elevated BP, hypertensive crises, and vasospasm, which potentially can increase the risk of ICA rupture. Numerous case reports have been made of use of cocaine and other drugs of abuse leading to AKI requiring dialysis that may not always resolve.[732,734] Illicit drug use and chronic misuse of anabolic steroids are also strongly associated with increased risks of CKD and kidney failure.[733,741–745]

People should be asked intermittently about their use of recreational drugs and anabolic steroids, as they may change

their usage (e.g., starting, stopping, or increasing intake) at any time during their lives.

Research recommendations

- Studies are needed to assess the risks versus benefits of using cannabis products for relief of chronic pain and other symptoms in ADPKD.
- Epidemiologic studies are needed to analyze the association of specific nephrotoxins with outcomes of ADPKD.

7.4 Psychosocial care

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

People with ADPKD and their parents and siblings are subject to a range of psychosocial stressors, following diagnosis and throughout their life, both before and after development of kidney failure (Figure 43). Some may need psychological interventions and/or referral to social care services.[746,747] Therefore, healthcare providers should consider working with accredited psychology or psychiatry providers to help those who develop mental health problems.

Anxiety and depression. Anxiety and depression are highly prevalent in people with CKD and are reported by >60% of those with ADPKD.[300] 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.[748,749] The occurrence of anxiety over an uncertain future should be anticipated in young people before and after presymptomatic testing and/or diagnosis.[750]

Healthcare providers may underestimate and overlook psychological issues in people with ADPKD, especially in its early stages.[751] However, healthcare providers caring for these people need to understand that many people are having thoughts such as the following: *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?*; and *Will anyone want to marry me with ADPKD?*[747] 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.[752]

If ignored, psychosocial issues can lead to a socioeconomic burden for people that stems from career and financial planning decisions that could negatively impact individuals and their families for years to come. Therefore, healthcare teams should be aware of the psychological support needs of people with ADPKD in different stages of life.[746,753]

The burden and uncertainty of ADPKD affect patients and their families throughout the disease's progression, from screening, to KRT, and beyond. People with ADPKD face significant concerns about their long-term health and life expectancy, which can diminish their QoL (Table 20).[754,755]

Healthcare providers are essential in delivering genetic counseling, psychological support, and education, to help alleviate the uncertainty and anxiety that people with ADPKD and their families face. Crucial elements of this relationship

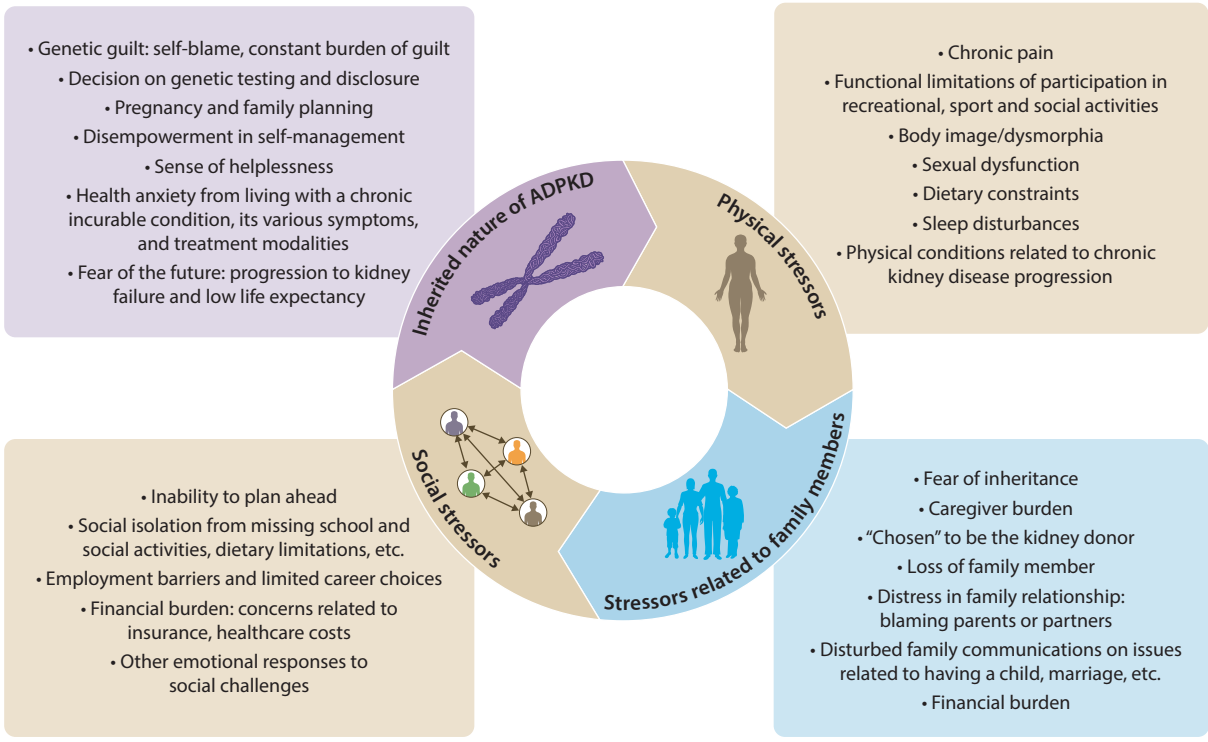


Figure 42 | Stressors associated with psychosocial issues in people with autosomal dominant polycystic kidney disease (ADPKD).

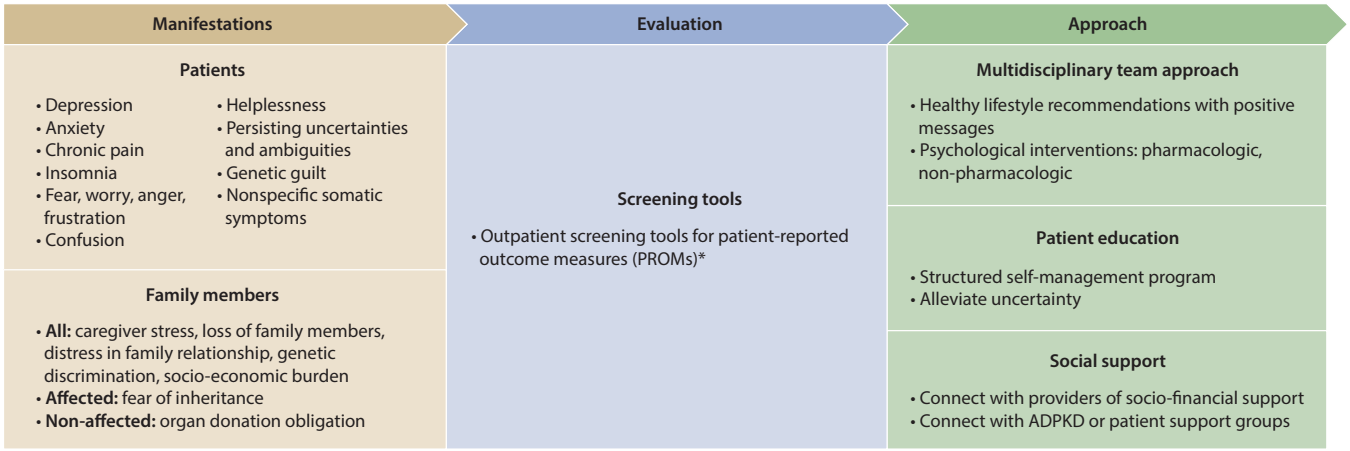


Figure 43 | Psychosocial manifestations, screening, and approach. ADPKD, autosomal dominant polycystic kidney disease. *See Appendix 1.

include offering psychological support, enhancing health literacy, and empowering patients to actively participate in identifying the most effective treatment options.

No guidelines specify the appropriate timing and/or interval of psychological screening in people with ADPKD. However, given the prevalence and its diverse manifestations, annual review of these would be prudent. Standardized, preclinic-visit, and planning tools for screening and identifying psychosocial issues in people with ADPKD should be considered (Appendix 1).

Body image and sexual dysfunction. As ADPKD progresses, many changes happen to a person that can have negative impacts on their body image and sexual functioning.[746,756] Concerns about body image are linked to anxiety and depression.[757] Some people with an enlarged or deformed abdomen linked to cystic kidneys or liver, for instance, experience negative body-image issues that can affect their sexual functioning. Many people have reported feelings of being "defective" or "ugly," including fears of being rejected by their partner.

Normal sexual functioning 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 issues. Multiple studies have shown how a negative body image can lead to sexual dysfunction.[758–762] The sexual dysfunction itself, which could be caused by medication or other ADPKD effects, can lead to mental health issues, including depression. Sexual-function abnormalities are observed frequently in men with CKD G4–G5.[763]

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 not only those people with ADPKD, but also non-affected members of the family, including parents and siblings, is a unique feature in inherited diseases, including ADPKD.[749,751] Appropriate education about genetic diseases ("genetic literacy"), and counseling, should be provided to people with ADPKD and their family members (Chapter 1).

Chronic pain. Chronic pain is a common cause of psychosocial issues in people with ADPKD. Studies have shown that chronic pain impacts 60% of people with ADPKD. Healthcare providers should include a psychosocial approach

Table 20 | Key concerns of people with ADPKD and their family members, relating to psychosocial issues

Theme	Description
Life expectancy and health management	• Uncertainty regarding the progression of ADPKD and its effect on longevity • Complexity due to varying clinical presentations and disease manifestations between and within families
Relationship with family members	• Concerns over the hereditary nature of ADPKD affecting children and its influence on long-term relationships and marriages • Familial experiences with ADPKD can lead to anxiety or resentment toward parents
Relationship with society	• Risk of workplace discrimination stemming from an ADPKD diagnosis • Difficulties in securing life insurance, with patients often classified as "high risk"
Future planning	• Unpredictability in necessary medical interventions (such as dialysis or transplantation) and clinical variability • Uncertainty in decisions regarding family planning and careers, affecting long-term personal and professional life planning
Interaction with the healthcare system	• Disparities between patient experiences and medical assessments of symptom severity • Frustration over insufficient information and lack of clarity provided by healthcare providers

ADPKD, autosomal dominant polycystic kidney disease.

for the management of chronic pain that is intense and repeated in nature and has not responded to initial medical and/or surgical treatment.[764] The appropriate initial therapeutic strategy for chronic pain of a psychological origin depends upon an accurate evaluation of the cause of the pain and the type of chronic pain syndrome. Chapter 2 discusses pain in detail; healthcare providers should discuss with people how chronic pain is 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.[752] Key objectives of self-management education are as follows:

- to improve ADPKD-related knowledge;
- to improve self-management and self-motivation;
- to encourage the adoption and maintenance of a healthy lifestyle; and
- to improve emotional and mental well-being, treatment satisfaction, and QoL.

Learning needs also should be monitored regularly.[765] Figure 44 summarizes information for people with ADPKD and their 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 via provision of information; identification of sources of financial support and assistance; and peer support. These organizations and groups exist in many countries. For a partial list of those supporting people with ADPKD and their families, see Appendix 3 or 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 help them avoid incurring unnecessary medical expenses.

Healthcare providers may underestimate the financial burden placed on people with ADPKD,[767] and if it is not discussed, people may feel isolated, resulting in missed appointments, reluctance to undergo 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, and the costs of medications, relative to their expected benefits, should be discussed. Healthcare teams should provide country-specific information on sources of financial support for medications, KRTs, and caregiver needs, as well as legal protection against

Disease information	• Explanation of the disease and its potential course and manifestations
Basic management and self-care	• Self-management: water intake, low-salt diet, low-protein diet (where appropriate), weight control, lifestyle (e.g., exercise), smoking cessation, caffeine intake, etc. • Cardiovascular risk management: importance, antihypertensive therapy, cholesterol-lowering therapy • Situations for contacting clinic (e.g., pain, complications)
Prognostic assessment	• Rationale, interpretation and implications of prognostic risk score
Specific kidney-protective pharmacotherapy	• Indication, rationale/benefit, adverse effects, monitoring requirements • Clinical trial opportunities
Managing disease impact	• Potential impact of the disease on activity (e.g., work and lifestyle) • Psychological impact and support available • Discussing ADPKD with employers • Issues regarding health insurance and mortgage applications • Family planning, including genetic counselling and preimplantation genetic diagnosis, contraception, and pregnancy issues
Kidney replacement therapy	• Dialysis and transplantation options (according to clinical situation and availability)
Research	• Registry entry, clinical trials, patient-reported outcome data collection
Resources for social support	• Details of financial burden of ADPKD and how to get socio-financial support • Details of ADPKD patient organizations
Hereditary nature of ADPKD	• The most common hereditary kidney disease and its genetic transmission • Importance of kidney imaging in the diagnosis of ADPKD • Possible benefits and harms of genetic screening (Practice Points 1.3.1, 1.3.2, Table 3)

Figure 44 | Information for people, caregivers, and families affected by autosomal dominant polycystic kidney disease (ADPKD). Reproduced with minor modification from European ADPKD Forum (EAF) Co-chairs *et al.*[766]

discrimination regarding employment, mortgages, and life and health insurance.[768]

Research recommendations

- Studies are needed to validate and 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 is needed, including analysis of differences in geographic, cultural, and other demographic factors.
- Studies are needed to assess the effects of body dysmorphia on mental health and sexual dysfunction in people with ADPKD.
- Studies are needed to assess various interventions to improve 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 their age at diagnosis.
- Research is needed to develop and evaluate online tools that allow people with ADPKD to quantitatively assess the impact of issues such as body image and sexual dysfunction on their psychosocial well-being, taking into account cultural and regional variations.
- Studies are needed to assess the financial and societal burden of ADPKD, to inform policy and coverage decisions, and 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 including contraception, preconception counseling, and pregnancy management (Figure 45).

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

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

Contraception is achieved using hormonal (estrogen-based, progestin-based, or combined hormonal contraception) or nonhormonal methods. A finding that is generally accepted is that estrogens promote the progression of PLD, which itself is more severe in women than in men. Liver volume increases in premenopausal women but stabilizes postmenopause. Estrogen replacement after menopause is associated with an increase in liver volume, compared to the volume in women with ADPKD who are not taking estrogens.[495,517,519] Although data are limited, exposure to estrogen-containing contraceptives is associated with greater liver volume in women with ADPKD.[518] Animal studies demonstrate that estrogens stimulate proliferation of intrahepatic biliary epithelium in rats.[769] The severity of PLD varies widely among people with ADPKD. PLD has been found to be minimal or very mild even in women with many pregnancies or years of exposure to estrogen-containing contraceptives.[518] 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 (see 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.[770] Combined oral contraceptives containing low levels of estrogens (10–35 μg ethinyl estradiol) generally are preferred. Patches and intravaginal rings avoid the first-pass liver effect and may have less impact on PLD. An advantage of the patch is the steadiness of estrogen levels, without the peaks and troughs seen with oral contraceptives; however, the total estrogen dose is higher. Intravaginal rings allow for lower serum estrogen concentrations than those that occur with pills or patches.

Progestin-only methods include pills, injections, implants, and intrauterine devices (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.[771] Progestin-only contraceptives also could stimulate the growth of cysts in the livers of people with ADPKD. However, progestin-only contraceptives have been shown to inhibit the growth of hepatocellular adenomas and estrogen-containing contraceptives to stimulate their growth, despite the expression of both progesterone and estrogen receptors in these lesions.[772] The impact of progestin-only contraceptives on liver volume in

Women with ADPKD of childbearing age

Hormone therapy	Preconception counseling	Management during pregnancy	Management after pregnancy
• Counsel about risk/benefit of estrogen/progesterone therapy in ADPKD women with regard to PLD	• Discontinue potential teratogenic drugs before becoming pregnant (e.g., tolvaptan, RASi)	• Regular monthly assessment of BP, kidney function, and proteinuria by a health care provider	• Tolvaptan is contraindicated during breastfeeding and should not be prescribed during this time
• IUDs (including levonorgestrel-releasing IUD) and gestagen OCPs may be preferred for women with PLD	• Review the risks of preeclampsia, pregnancy induced hypertension, and premature delivery in ADPKD women	• Home BP monitoring is encouraged • Suggested target BP <135/85 mm Hg	• Some ACEi such as enalapril or captopril have very low penetration into human milk and can be used with careful monitoring of the infant for signs of hypotension, if other agents are not adequately controlling blood pressure.
	• Genetic counseling. Information on risk of inheritance of ADPKD for each pregnancy, nature of fetal/childhood outcomes in affected offspring, and the potential risk/benefit of PGT/PT/egg-sperm donation	• Low dose of aspirin from week 12 to week 36 is recommended for all pregnant ADPKD women • Monthly screening for UTI is advised. Those with positive urine cultures should be treated adequately • Encourage increased fluid intake	• Women with bladder instability or urinary incontinence after pregnancy should be offered pelvic floor physical therapy, especially when tolvaptan will be prescribed

Figure 45 | Management of women with autosomal dominant polycystic kidney disease (ADPKD) of childbearing age. ACEi, angiotensin-converting enzyme inhibitor; BP, blood pressure; 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 system inhibitors; UTI, urinary tract infection.

people with ADPKD is not known and is an important topic for future research.

Nonhormonal contraception methods that are completely free of exogenous estrogens include barrier-based forms of contraception (condoms, diaphragms, cervical caps, contraceptive sponges, and vaginal spermicides), 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 the barrier-based options and lowest for IUDs.[773]

Because of the low chances of a significant effect on liver cystic disease, and the high impact of an unwanted pregnancy, contraception should not be restricted in adolescents and young adults.

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.[519] Alternatives to estrogens or progesterone should be encouraged in those with ADPKD and severe PLD.[774,775]

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

Decision-making regarding the use of hormone therapy should include consideration of the presence and severity of PLD; however, no staging system for disease severity has been established so far. Although the advised approach is to minimize the use of oral contraceptives containing estrogens, and possibly progestins, in people with PLD, when they are prescribed, monitoring of their effects on PLD via regular imaging follow-up of the liver from adulthood seems wise.

8.2 Preconception counseling

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

Preconception counseling for ADPKD addresses a range of topics, including medication adjustments for women, reproductive options, potential pregnancy outcomes, and the distinct risks anticipated for both a mother and a child who is at risk of inheriting the condition.

Preconception counseling should be conducted by qualified providers and should consist of a shared decision-making process. Primary care physicians, nephrologists, and/or genetic counselors can be involved (Figure 46). The attitude toward various reproductive options in people with ADPKD will vary based on individual values, medical availability, and potential intrafamilial variability of disease severity.

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

Prenatal testing of the fetus. The purpose of prenatal testing is to determine whether the fetus has ADPKD. This technique can be offered only if the parental causal pathogenic deoxyribonucleic acid (DNA) variant is known. This option should be offered to only those parents who would consider pregnancy termination and/or abortion (with considerations 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 pregnancy loss, and spontaneous miscarriage occurs in approximately 1% of pregnancies. Prenatal cell-free DNA screening, which is available from week 10 of gestation, involves detection of fetal cells in maternal blood, but no evidence is available regarding 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. 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 to only those families with a confirmed causal pathogenic variant who accept 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.[776,777]

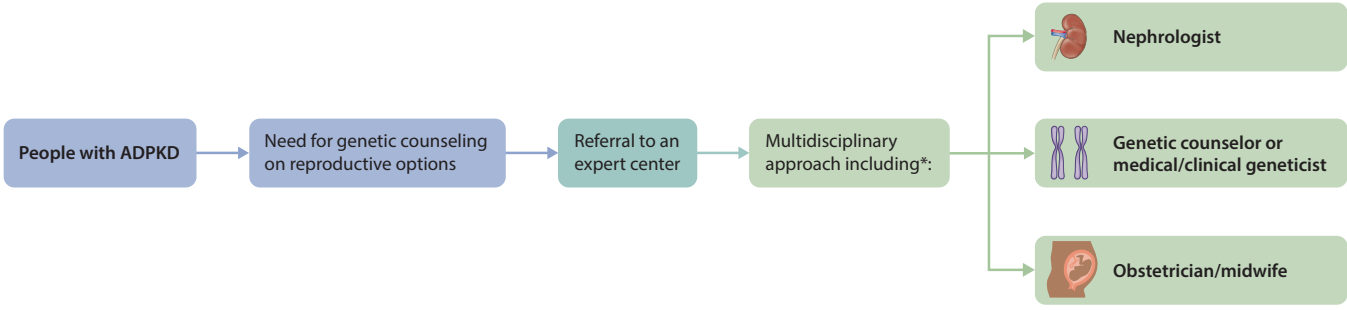


Figure 46 | Multidisciplinary approach to preconception counseling. ADPKD, autosomal dominant polycystic kidney disease. *Other specialties may be involved, depending on the case (e.g., hepatologist, neurologist).

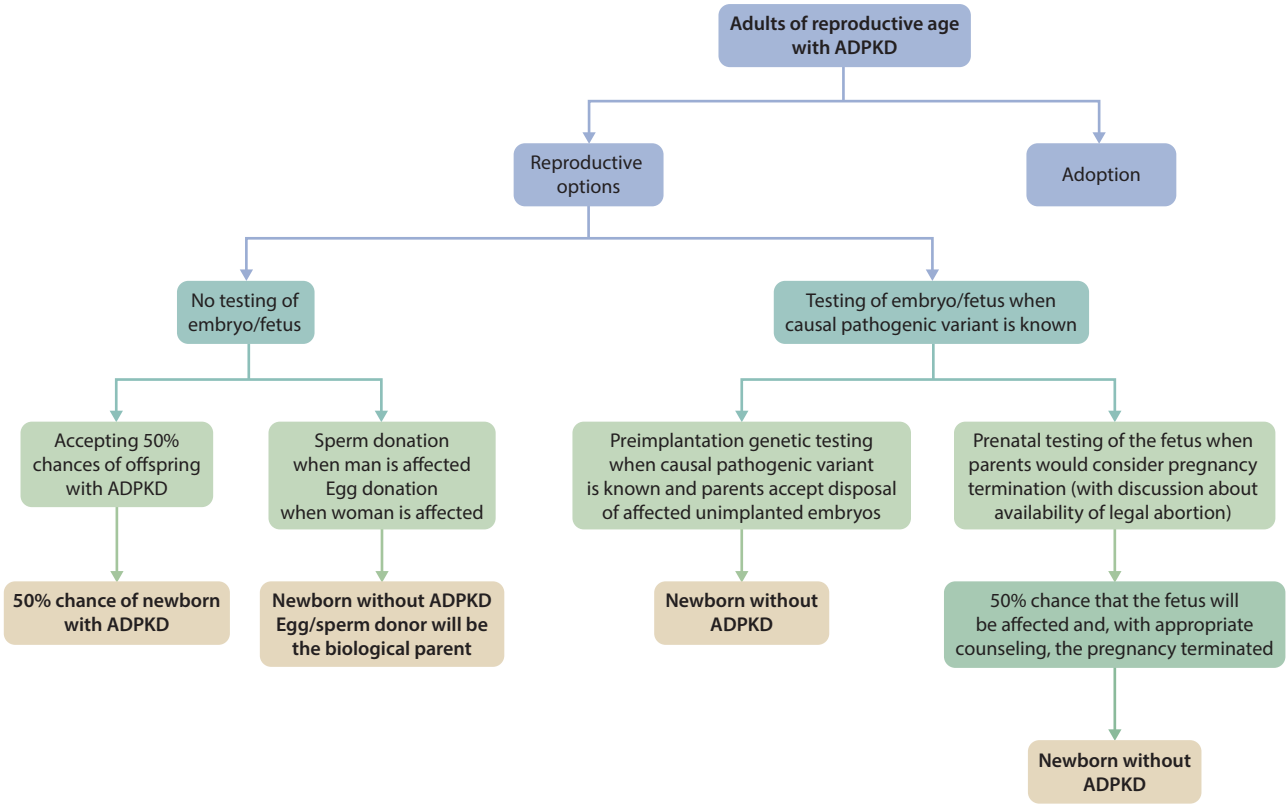


Figure 47 | Reproductive options for men and women with autosomal dominant polycystic kidney disease (ADPKD).

Ovarian stimulation for IVF requires high doses of hormones that may increase cyst growth in women with PLD, and it 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/or 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, only limited data are available to evaluate this possibility. The chances of a successful pregnancy occurring with use of PGT in monogenic diseases is approximately 30%.[778] Given that a sufficient number of embryos are required for genetic analysis, and that approximately half of the embryos would carry ADPKD mutations, an important point to note is that the rate of embryos produced per cycle diminishes with advancing maternal age. After the initial ovarian stimulation, embryos that have tested negative also can be stored for another round of IVF if the parents are considering having another child. Consequently, an advisable approach is to initiate discussions about the viability of PGT early in the reproductive journey, ideally before the female partner reaches age 35 years. As in the general population, the live-birth delivery rate with IVF significantly declines with female age in ADPKD, as it does in the general population.[779]

The uptake of PGT for ADPKD is growing worldwide,[778] although some groups disapprove of using this procedure, which also is not widely available throughout the world. In some countries and regions, the cost of the procedure is covered by the public health system or insurance, whereas in others, it is extremely expensive or has a very long waiting list.

Artificial insemination by sperm donation. Artificial insemination with donor sperm involves controlled or stimulated ovulation, with placement of the donor's sperm inside the uterus on the day of ovulation. This reproductive option is one to consider when the male partner has ADPKD. In the case in which an unaffected male partner is infertile, sperm donation would entail less risk of worsening PLD in an affected female partner, as hormonal-therapy doses are much lower than those 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 (mostly those that are autosomal recessive and X-linked), chromosomal abnormalities, and sexually transmitted infections that can 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 in cases in which a female partner has ADPKD. However, given the fact that this procedure involves IVF, the rate of uptake of this option is very low in those with ADPKD when PGT is available. Egg donation could be useful in cases involving women with severe PLD in which IVF is discouraged, as when PGT is not possible due to low ovarian reserve,

or when a causative mutation cannot be identified. Couples should be advised that in cases in which the pregnancy goes to full term, the egg donor will be the biological mother of the baby.

If these reproductive options are not preferred or are not viable or effective, discussion about the benefits of adoption and surrogacy is advisable.

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

Only minimal observational data are available in human pregnancy to help determine if a risk of adverse developmental outcomes is associated with use of tolvaptan; therefore, this drug is considered a class-D drug in pregnancy. In animal studies, tolvaptan use was shown to cause cleft palate, brachymelia, microphthalmia, skeletal malformations, decreased fetal weight, delayed fetal ossification, and embryofetal death. Tolvaptan is transferred to breast milk; therefore, its use during periods when breastfeeding is taking place is contraindicated. Women of childbearing age should use adequate contraceptive measures during treatment with tolvaptan. Tolvaptan use 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 their use is not advised, because of their potential fetal toxicity. The best approach is to stop use of these medications in women who are planning a pregnancy, and if necessary, to change to use of 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.[772] Use of these agents needs to be stopped, and if necessary, a switch made to other antihypertensive medications for the duration of the pregnancy. Some ACEi, such as enalapril or captopril, have very low levels of penetration into human milk and, based on limited evidence, can be used safely if other agents are not controlling BP adequately.[780]

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

Studies have demonstrated that a higher prevalence of seminal tract cysts and sperm abnormalities (necrospermia, ultrastructural flagellar defects, and immotile sperm) occurs in men with ADPKD. However, these issues rarely are associated with male infertility.[678,781] Whether the frequency of male infertility in ADPKD is higher than that in the general population is not known, but the frequency does not appear to be high enough to warrant a systematic preconception evaluation.

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

No evidence indicates that the risk for ICA rupture is increased during pregnancy or vaginal delivery. Systematic screening for ICA before pregnancy or delivery in women with ADPKD usually is not performed. Nevertheless, screening for ICA is advised in the same circumstances for these women as for any person with ADPKD (Chapter 6). If an ICA is found, decisions regarding need, timing, and type of intervention should be made by specialized neurosurgeons or interventional radiologists. No evidence is available to alter established BP targets 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 a maternal–fetal medicine specialist and a nephrologist. However, in certain circumstances, other specialists, such as hepatologists and neurologists, may be needed. Given the potential risks of pregnancy and the need for a multidisciplinary team, an advisable approach is for the pregnancy to be followed by—either fully or in collaboration—a medical center with expertise in ADPKD and pregnancy, or CKD and pregnancy.

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

No specific evidence indicates how to best manage BP in people with ADPKD during their pregnancy. Although most women of childbearing 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.[782] These guidelines may be used in the setting of pregnancy in ADPKD.

Kidney function in pregnancy is assessed using measures of SCr level. Mean values for SCr level in pregnancy are 84%, 77%, and 80% of the mean values for nonpregnant people, during the first, second, and third trimesters, respectively.[783] Quantification of proteinuria is undertaken by measuring

the urine protein-to-creatinine ratio or the urine albumin-to-creatinine ratio. This process should be done regularly (tailored to the severity of CKD; if eGFR>90 ml/min per 1.73 m^2, the same regular pregnancy laboratory tests should be ordered that are ordered in healthy women), in conjunction with home BP-monitoring, as opposed to office BP-monitoring, if possible. A 24-hour urine collection for quantification of proteinuria is not required.

Angiogenic and antiangiogenic factors have become essential tools for accurately predicting and diagnosing preeclampsia, showing a high level of precision in clinical use (see Practice Point 8.5.1)

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

A review of the evidence from the U.S. Preventive Services Task Force concluded with a moderate grade of certainty that screening for and treating asymptomatic bacteriuria in pregnant women has a moderate net benefit in reducing perinatal complications, and that treating screen-detected asymptomatic bacteriuria can reduce the incidence of pyelonephritis in pregnant women.[784] The recommended approach is 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.[785]

Women with ADPKD have a 14% greater risk of UTI during pregnancy, compared with people without ADPKD.[786] The risk is higher in people with greater htTKV.[787] UTIs increase the risk of spontaneous labor and preterm delivery in the general population.[788] Therefore, treatment of UTI is important and should be done quickly after a positive culture has been obtained. Women with ADPKD and a positive urine culture, in the absence of increased temperature or signs of cyst or 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 perform vaginal delivery safely.

No evidence indicates that TKV or kidney transplantation impacts the preferred type of delivery.

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

Pregnant women can undergo ultrasound or MRI safely in any trimester, and no evidence indicates that these procedures cause harm to the fetus. Although routine obstetric ultrasound is performed regularly during pregnancy, this procedure typically is done to evaluate the fetus and not maternal abdominal organs, such as the kidneys.

8.4 Hypertension in pregnancy

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

Gestational or pregnancy-induced hypertension is more frequent in women with ADPKD than in unaffected women.[786,786] Regular monitoring of BP throughout pregnancy is prudent. No direct evidence has been gathered from 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.[215,789]

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

Although they are 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; second- or third-line agents include hydralazine and prazosin.[790–792] RASi are contraindicated, and diuretics should not be used to treat high BP in pregnancy.

Decisions regarding the initiation of antihypertensive therapy during pregnancy in women with ADPKD should be made with consideration of 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 (to <110/75 mm Hg) in young people with ADPKD, these benefits are long-term, impacting the rate of increase in TKV and decline in eGFR over 5 years in a nonpregnant population.[205] Given the relatively short time interval of pregnancy, with the known hemodynamic changes that occur to maximize placental blood flow and perfusion, the BP target in pregnant women with ADPKD is ≤130/85 mm Hg.[782]

8.5 Preeclampsia

Practice Point 8.5.1: Women with ADPKD are at an increased risk of preeclampsia and preterm delivery and should be monitored carefully throughout their pregnancy and in the postpartum period. Assessment of the sFlt-1/PlGF ratio in plasma, from 24 weeks of gestation and every 4–6 weeks, should be done to rule out preeclampsia.

Preeclampsia, classically considered to be the clinical presence of increased BP, proteinuria, and edema, can lead to poor pregnancy and perinatal outcomes. Preeclampsia is more common in women with ADPKD than in the general

population.[786,793] Preeclampsia 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.[794,795] The condition 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 a known cardiovascular risk factor. Although the relationship between the development of preeclampsia and future kidney failure in women with ADPKD has not been studied, preeclampsia in all forms of CKD has been found to be associated with an increased risk for kidney failure.[795]

Although 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.

Angiogenic and antiangiogenic factors have emerged as indispensable tools for the prediction and diagnosis of preeclampsia, demonstrating high accuracy in clinical applications. Rooted in the pathophysiology of the disease, these factors have proven to be reliable in forecasting and identifying preeclampsia. Notably, the clinical utility of 2 specific cutoff values has been assessed rigorously. According to findings from the Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia study, employing an sFlt-1/PlGF ratio cutoff of 38 enables the exclusion of preeclampsia for 1 week, with a very high NPV (99.3%, 95% CI: 97.9%–99.9%), although a low PPV (36.7%, 95% CI: 28.4%–45.7%).[796] Separately, a diagnostic cutoff of 85 has exhibited high accuracy in identifying women with preeclampsia; delivery occurred within 2 weeks of presentation in 86.0% of women with an sFlt1/PlGF ratio ≥85, compared with 15.8% of women with an sFlt1/PlGF ratio <85 (HR: 15.2; 95% CI: 8.0–28.7).[797] This review underscores the pivotal role played by angiogenic and antiangiogenic factors in the differential diagnosis of women at elevated risk of preeclampsia, particularly those with preexisting conditions, such as chronic hypertension and CKD. In a recent study in women with CKD and suspected superimposed preeclampsia, severe angiogenic imbalance was associated with confirmed superimposed preeclampsia or progression to superimposed preeclampsia. Patients with no angiogenic imbalance displayed lower rates of progression to superimposed preeclampsia, whereas outcomes were intermediate, supporting a systematic use of the sFlt-1/PlGF ratio, and other biomarkers in the clinical management of CKD pregnancies.[798] Unfortunately, the utilization of these tests is limited by their availability.[799]

Figure 48 shows the clinical signs and symptoms of preeclampsia with versus without proteinuria. Note that not all signs and symptoms need to be present in women with preeclampsia.

Blood pressure

- Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
- Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more (severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy)

and

Proteinuria

- 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection)

or

- Protein/creatinine ratio of 0.3 mg/mg (30 mg/mmol) or more

or

- Dipstick reading of 2+ (used only if other quantitative methods not available)

Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia: platelet count less than 100×10^9/l
- Abnormal kidney function: serum creatinine concentrations greater than 1.1 mg/dl [97 µmol/l] or a doubling of the serum creatinine concentration in the absence of other kidney disease
- Impaired liver function: elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Figure 48| Diagnostic criteria for preeclampsia from the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 222.[793]

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. Only minimal data are available 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 even at higher risk for preeclampsia if they have preexisting hypertension or abnormal kidney function. Therefore, consistent with international guidelines for pregnancy,[782,793] women with ADPKD should take 75–150 mg of aspirin daily, preferably at bedtime, starting at 12 weeks gestation (preferably starting at no later than 16 weeks), until they have reached 36 weeks of gestation.

The benefit of low-dose aspirin use needs to be balanced against its potential harm. A retrospective analysis of 663 people with ADPKD in the Developing Interventions to Halt Progression of ADPKD (DIPAK) observational cohort showed that use of aspirin (325 mg/d) was associated with a 2-fold higher frequency of macroscopic hematuria in men and nonpregnant women.[800] Nevertheless, the overall risk was low, and the episodes of macroscopic hematuria were self-limited. These data suggest that the benefit of aspirin use for prevention of preeclampsia outweighs the risk of cyst bleeding, especially at the suggested low dosages.

8.6 Fetal evaluation for ADPKD

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

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

Features that occasionally are seen on prenatal ultrasound, including enlarged echogenic kidneys, abnormal corticomedullary differentiation, and/or kidney cysts, are not specific to ADPKD. Although 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 are likely to indicate an eventual diagnosis of ADPKD in the fetus.

The mere detection of prenatal findings suggestive of ADPKD does not necessarily reflect postnatal disease severity,[801] as with serial monitoring; such children may show normalization of kidney size and limited progression in early childhood. If a definitive diagnosis is required, genetic testing is confirmatory. However, extensive fetal cystic kidney involvement or evidence of abnormal kidney function in the fetus (e.g., oligoanhydramnios) portends poor postnatal and childhood outcomes.[802,803] Such severe cases may warrant proper genetic testing (Chapter 1).[68,70,804–806] Termination of pregnancy may be considered when significant fetal dysfunction leading to Potter sequence is present (i.e., atypical physical appearance of a baby due to oligohydramnios, including clubbed feet, pulmonary hypoplasia, and cranial anomalies). However, the latter 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 level of 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 have kidney cysts of sufficient size to be detected by current ultrasound resolution. Therefore, in an at-risk fetus, an important point to convey to parents is that a normal kidney ultrasound in fetal life, or even in childhood, does not exclude the diagnosis of ADPKD (see Chapters 1 and 9).[460]

8.7 Postpartum care

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

Estimated GFR typically returns to pre-pregnancy levels at a point in time toward term, or shortly after delivery.[783] BP, which typically declines during pregnancy, will increase after delivery and preferably HBPM should be performed. BP control after delivery should target <110/75 mm Hg in women aged 18–49 years with an eGFR >60 ml/min per 1.73 m^2, based on the findings of the HALT-PKD trial (Chapter 2).[205] For women with more advanced CKD (CKD G3–G5), a mean SBP of <120 mm Hg should be targeted (Chapter 2). 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 if tolvaptan will be prescribed.

Bladder instability and urinary incontinence are quite frequent (occurring in approximately 15% of instances) after

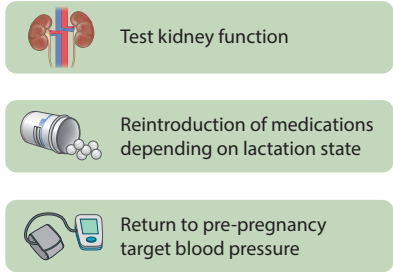


Figure 49 | Postpartum kidney review.

pregnancy in women.[807,808] Nephromegaly, hepatomegaly, and the habit of drinking large volumes of water, which are present in many pregnant women with ADPKD, may increase the risk of urinary incontinence. Although pelvic floor physical therapy is advised for bladder instability postpartum in all women, it may play a particular role in women with ADPKD who plan to take tolvaptan, considering that the drug will cause polyuria, often with nocturia.

Research recommendations

- Sufficiently powered epidemiologic studies are needed to determine the risk for preeclampsia in women with ADPKD, especially those with CKD G1 and no hypertension. Such work should consist of 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, htTKV, and MIC on the need for special delivery procedures, risk of cyst bleeding, and pregnancy outcomes needs further research. Studies should be multicenter, cooperative, and prospective in nature, and they 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 the impact of 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. Such work should consist of multicenter, cooperative, prospective studies of ADPKD pregnancies, assessing the impact of screening, BP control, and type of delivery on ICA rupture.
- Studies are needed to determine a safe target level of BP control for people with ADPKD during pregnancy.
- Studies are needed to determine the appropriate use of circulating angiogenic factors (sFlt-1 and PlGF) for early detection of preeclampsia in ADPKD. Specifically, such work should be a multicenter, cooperative, prospective study assessing the value of circulating angiogenic factors (sFlt-1 and PlGF) for early detection of preeclampsia.
- Studies are needed to assess the barriers for access to PGT, and the reliability of *PKD1* mutation detection in PGT. This work should include a survey of people with ADPKD and physicians, evaluating their awareness and attitudes toward 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 identifying women with ADPKD who become pregnant is needed.

Chapter 9: Pediatric issues

Appropriate interventions for children with or at risk for ADPKD are lacking, as currently, neither validated stratification models exist to identify children at risk of rapid progression, nor are there any approved therapies specifically for this population.[809,810] Therefore, this chapter aims to harmonize current practices for care of children with, or at risk for (potential heritability in the setting of an affected relative), ADPKD, and highlight the gaps and 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 rarely are seen early in life. Very-early-onset (VEO)-ADPKD and early-onset (EO)-ADPKD forms of ADPKD are rare and distinct subentities of ADPKD (Table 21).

Although clinical complications of ADPKD may not be evident in childhood, structural kidney disease is present from early in childhood and may even be evident on antenatal imaging.[811] A wide variability of phenotypical ADPKD presentations exists early in life. Rarely, children present with severe clinical features that mimic 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.[69,70,812–816]

No validated definition of disease progression in children with ADPKD is available. VEO-ADPKD and EO-ADPKD entities were proposed in the 1990s and 2000s. These are clinical definitions that do not reflect the impact of genetic modifiers or mutational load, and the criteria for VEO-ADPKD and EO-ADPKD have not been consistent across studies.[6,116,802,803,814,815,817] Proposed definitions are included in Table 21. A critical point to note is that these higher-risk entities are accompanied by clinical findings (e.g., hypertension, decreased eGFR, oligohydramnios); that is, the finding of enlarged kidneys alone at a specified age is not sufficient to warrant use of VEO or EO terminology.

VEO-ADPKD has been described as ADPKD diagnosed *in utero* with hyperechogenic enlarged kidneys (>2 SDs for gestational age) with oligohydramnios, or between birth and age 18 months with enlarged cystic kidneys (>2 SD for age, sex, height) with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR.[6,802,803,818]

EO-ADPKD has been described as ADPKD diagnosed between ages 18 months and 15 years, with enlarged cystic kidneys (>2 SD for age, sex, and height) between ages 18 months and 15 years, with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR.[6,116]

Children with VEO-ADPKD were shown to be more likely to develop hypertension and to progress to an eGFR <90 ml/min per 1.73 m^2 by adolescence, compared to people with ADPKD diagnosed during childhood.[803] The very severe phenotypes in early childhood are often due to combinations of mutations in ≥2 ADPKD genes, and therefore, they are rare (Chapter 1).

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

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

The volume of requests for counseling by families with children at risk for ADPKD is increasing as information on the disease is disseminated, and more data on children with ADPKD are emerging.[810,819,820] Multiple issues have to be considered in a counseling situation concerning a genetically dominant, slowly progressive disorder, of which many people

Table 21 | Definitions of phenotypical entities in children with ADPKD

Subentity	Definition
VEO-ADPKD	Symptoms or clinical evidence of severe ADPKD **at age <18 mo** defined by: • antenatal diagnosis of hyperechogenic enlarged kidneys (>2 SD for gestational age) with oligohydramnios, OR • enlarged cystic kidneys (>2 SD for age, sex, height) between birth and age 18 mo with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR
EO-ADPKD	Symptoms or clinical evidence of severe ADPKD **between ages 18 mo and 15 yr** determined by: • presence of enlarged cystic kidneys (>2 SD for age, sex, and height) between ages 18 mo and 15 yr with hypertension (BP ≥95th percentile for age, sex, and height) and/or decreased eGFR
Child with ADPKD	A child with diagnosis of **ADPKD not fulfilling VEO-ADPKD or EO-ADPKD criteria**
Child at risk of ADPKD	A child **with potential for heritability of ADPKD in the setting of a relative known to have ADPKD**

ADPKD, autosomal dominant polycystic kidney disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; EO, early onset; VEO, very early onset.

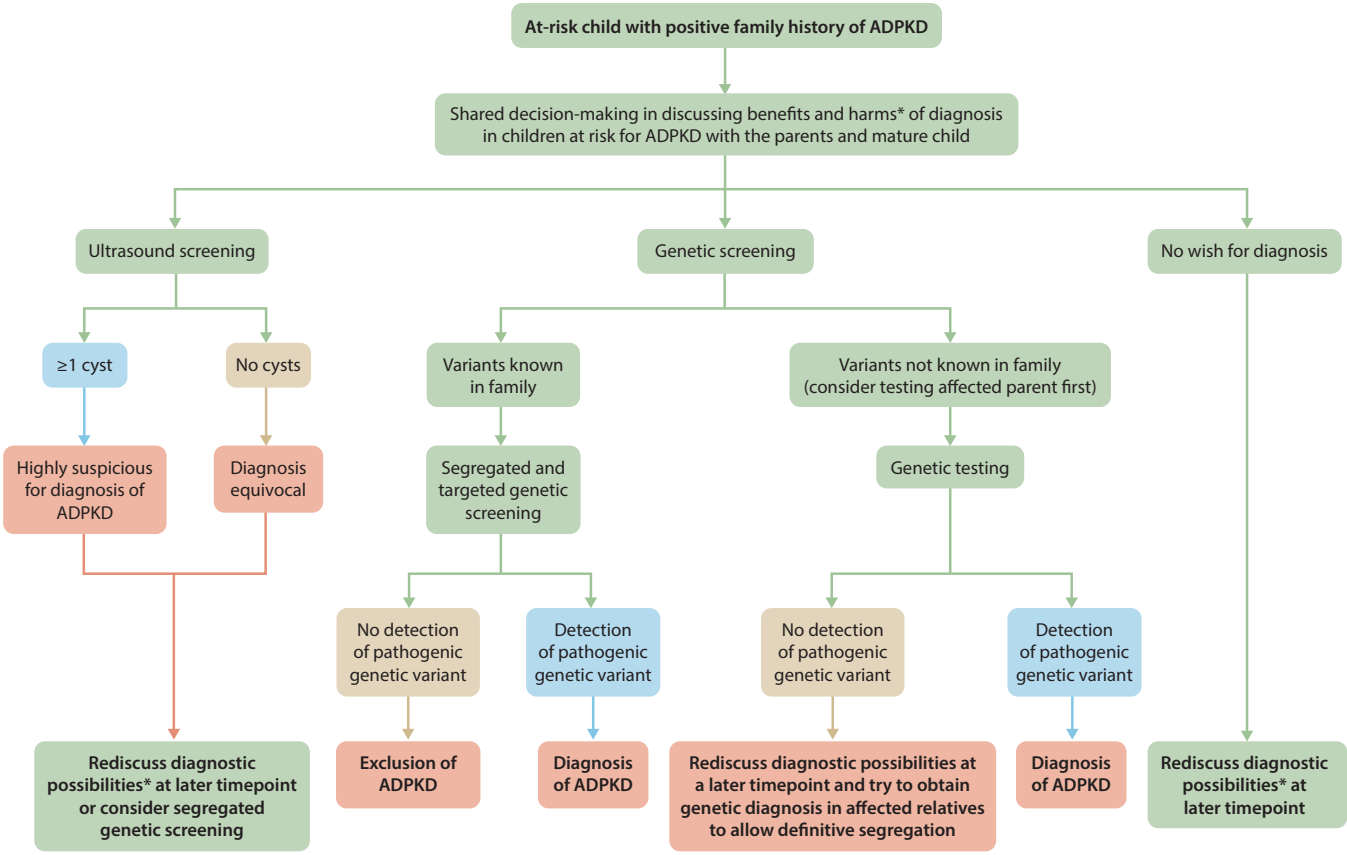


Figure 50| Diagnosis of children at risk of autosomal dominant polycystic kidney disease (ADPKD), which should be performed by a pediatrician with expertise in ADPKD. *See Table 3.

show no overt manifestations in childhood, including medical, psychological, cultural, ethical, socioeconomic, and legal aspects.[56,818,821] Approaches may vary according to the cultural background of the family; the family's beliefs, wishes, and preferences; family history; the healthcare providers; 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, one that includes the parents or legal guardians and the mature child. In younger children, information should be offered in an age-appropriate way. Of utmost importance is being aware of the possible different clinical courses of ADPKD, the specific psychosocial implications of early diagnosis for a child and family, as well as the potential clinical benefits and consequences of early diagnosis. Thus, counseling and empowerment of families regarding potential diagnostic steps in children at risk of ADPKD should be performed by a multidisciplinary team, including a pediatric nephrologist and geneticist or genetic counselor with expertise in ADPKD.[460,818] Guidelines for diagnosing ADPKD provide a consensus framework to use to approach children and adolescents with symptoms of or at risk for ADPKD.[460,818]

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

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

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

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

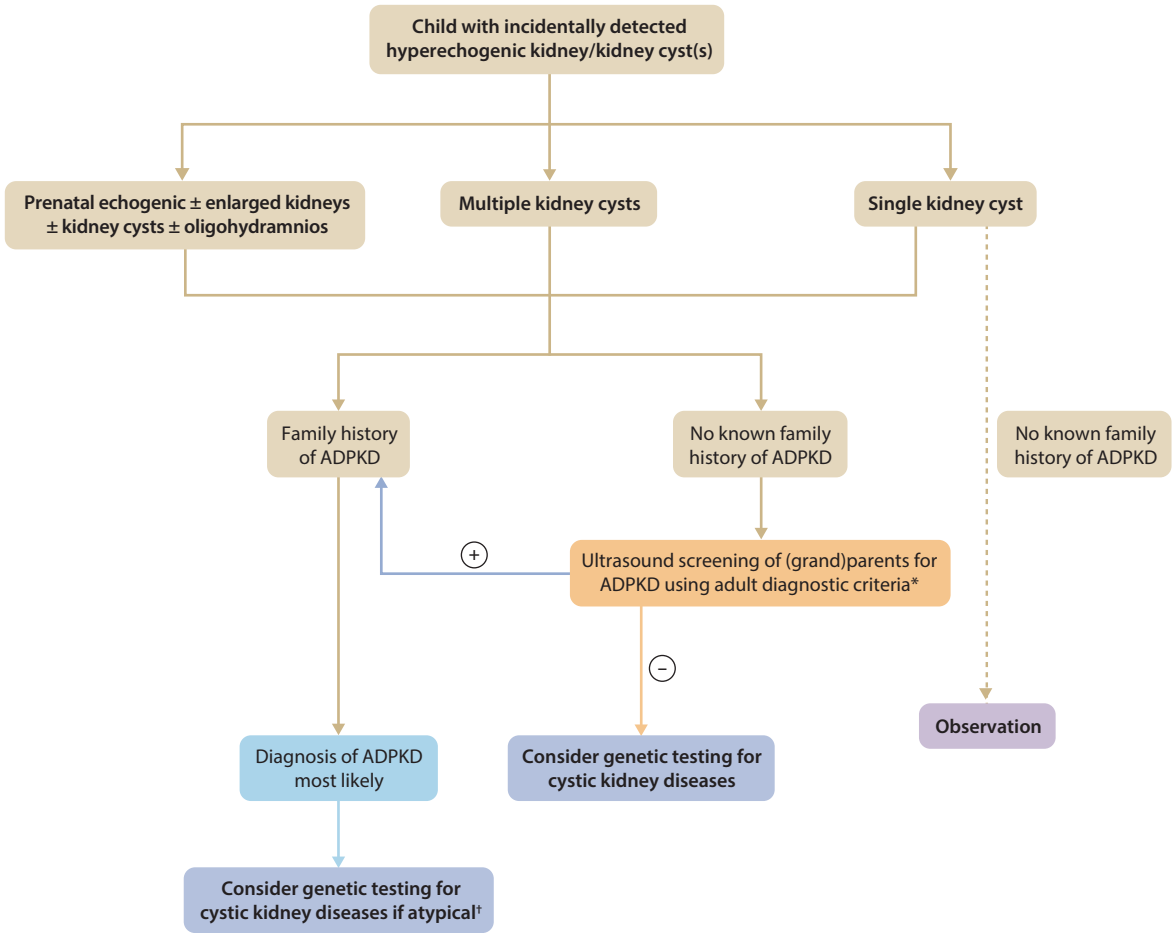


Figure 51 | Diagnosis of children with clinical consideration of autosomal dominant polycystic kidney disease (ADPKD). Dash lines denote other pathway for consideration. *Consider screening grandparents if parent screening is negative or parents are aged<40 years. †For example, very early onset ADPKD; severe kidney involvement relative to age.

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

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.[460,803,816,822–824] The detection of even a single cyst in children aged <15 years with a positive family history of ADPKD is highly suspicious for ADPKD,[818] as the incidence of simple cysts in childhood and adolescence is low.[825] Ultrasound examination of the parents of children with kidney cysts and a negative family history should be performed as a first step. Ultrasound findings in parents can help in finding the correct diagnosis for children, as they provide information on the mode of inheritance. Ultrasound findings for a grandparent may be helpful in a situation in which parents are aged <40 years, as in people with mild (undiagnosed) ADPKD, ultrasound may not show cysts when they are aged <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.[460]

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

Biallelic or digenic mutations may be present with more severe disease (VEO-ADPKD or more severe structural kidney disease relative to age). Atypical presentations of ADPKD also occur (e.g., multiple unilateral cysts evident before evolving to bilateral cystic kidney disease), or extrarenal cysts, such as liver cysts, autism, diabetes, etc., which would be unusual in childhood with a *PKD1* or *PKD2* mutation). In such cases, genetic testing can be of particular value to help clarify the diagnosis, prognosis, and potential for comorbid findings.

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

Genetic testing by state-of-the-art massive parallel sequencing techniques should be offered 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).[460] 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.[4,67–71,826,827] Genetic testing should cover PKD1 adequately, as described in Chapter 1. Furthermore, multiple additional genes for cystic kidney disease phenotypes for which analysis in a panel should be considered are 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 from birth, in children and adolescents with and at risk for ADPKD.

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

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

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

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

High BP (defined as a BP that is in ≥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 in this group than in the general pediatric population (<5%).[828–831] 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, as determined by ultrasound and MRI, has been observed consistently in children and young adults with ADPKD aged 4–22 years, a finding similar to those in older adults with ADPKD.[218,812,832] Children with ADPKD and BP in the high normal range (75th–95th percentile) or with BP in <75th percentile but with ≥10 kidney cysts by ultrasound have a high risk of developing high BP within the subsequent 5 years.[218] Moreover, children with ADPKD and high BP experience faster kidney growth and decline of kidney function compared to that of their normotensive peers.[218] Given that high BP is the primary treatable manifestation of ADPKD in childhood and has associated adverse implications for disease progression, routine monitoring of BP should be performed at least annually from birth, in children and adolescents diagnosed with or at risk for ADPKD. The finding of hypertension in a child at risk for ADPKD is an indication for further evaluation, including kidney imaging 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 mature people with ADPKD and their parents and/or guardians in this setting, prior to performing the examination.

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 LVMI in those with high BP.[832] Additionally, over 50% of affected children and adolescents with high-normal BP will develop high BP in a subsequent 5-year follow-up period.[218] Therefore, more detailed BP assessment is indicated in children and adolescents with ADPKD with a BP in >75th percentile. For children at risk of ADPKD with BP in ≥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 aged ≥5 years and who are ≥120 cm in height, and it is the preferred modality to diagnose high BP and evaluate antihypertensive efficacy in children.[833] 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 those with CKD.[834] Major advantages of ABPM include evaluation for white-coat hypertension and assessment of circadian BP patterns.[835] A significant proportion of children and adolescents with ADPKD manifest isolated nocturnal hypertension or a non-dipping pattern, which requires treatment but would not otherwise be identified by office BP measurement.[830] Indeed, isolated nocturnal hypertension with normal daytime BP has been observed in 16%–18% of children with ADPKD.[830,831] 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,[215] an ideal approach is to consider routine ABPM in children and adolescents with ADPKD with office BP in ≥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 the risk of progressive abnormal kidney function in children and adolescents with VEO- and EO-ADPKD,[802,803,818] more comprehensive assessment for high BP is indicated in these subgroups and ideally would be undertaken with annual ABPM, particularly with BP in ≥75th percentile. Guidelines for appropriate application of ABPM in childhood also have been published.[833,836] If ABPM

is not available, routine office BP-monitoring 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.[833] 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.

Practice Point 9.2.6: Perform echocardiography 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 an increased LVMI, as compared to the LVMI in healthy children and adolescents with an equivalent BP.[837] Also, a good correlation exists between both systolic and diastolic BP and LVMI in children and adolescents with ADPKD, even those who are within the normal BP range.[832] An important finding is that children and adolescents with ADPKD and BP in the high-normal range demonstrate an increase in LVMI similar to that of children and adolescents with ADPKD and high BP, and it is significantly higher than that of affected children with BP in <75th percentile.[832] 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 resolves appropriately.

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

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 antihypertension exposure for young people with ADPKD and greater associated risk of adverse drug effects and potential 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.[833] The HALT-PKD clinical trials demonstrated slowing of TKV growth in adults with ADPKD managed with rigorous control of high BP. A consistent and strong correlation exists between BP and TKV in children and young adults with ADPKD, throughout the normal range of BP,[69,831,832] as well as elevation in LVMI beginning in children with ADPKD with BP in >75th percentile. Based on these findings, a target BP of ≤50th percentile for age, sex, and height, or ≤110/70 mm Hg in adolescents appears to be 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 an increased occurrence of potential side effects (lightheadedness, dizziness, etc.). These risks should be discussed in advance with people with ADPKD and their families, before intervention is provided, and should be reviewed as treatment proceeds.

Certainty of evidence. Multiple studies in children and adolescents with ADPKD have confirmed the presence of a strong positive correlation between high BP and TKV.[218,457,828] A single small trial, with serious methodological limitations (due to high dropout rates and a lack of participant blinding) compared BP targets.[218] No studies in children and adolescents have compared various antihypertensive regimens. The grade of certainty of evidence for rigorous BP targets in children and adolescents with ADPKD and high BP was deemed to be very low.

Values and preferences. Limiting the rate of progression to kidney failure and other complications of ADPKD is critically important to people with ADPKD. Earlier intervention (i.e., in childhood) has been proposed to be of particular benefit to long-term clinical outcomes in ADPKD. BP can be monitored easily, and appropriate therapy adjustments made. Given these considerations, the Work Group surmised that despite the very-low grade of certainty of trial evidence specific to children with ADPKD, most, if not all, people with ADPKD (or parents and/or 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 BP-monitoring 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 people with ADPKD and their caregivers is important to outline appropriate therapeutic goals and 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. Rigorous control of high BP is indicated in the setting of LVH. 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 pharmacologic therapy for high BP in children and adolescents with ADPKD (*1D*).

This recommendation places a high value on the potential benefits of high-BP treatment with RASi over the benefit of other types of antihypertensive agents for slowing progression of abnormal kidney function and CVD in children and adolescents with ADPKD, and 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 about children and adolescents with ADPKD, the pathophysiology is believed to be similar to that of adults.[838] RAS blockade has a valuable role in mitigating glomerular hyperfiltration, a common and early feature of ADPKD in children and adolescents.[839,840] Targeting the 50th percentile BP, using RASi in children and adolescents with ADPKD and high-normal BP (75th–95th percentile), has been shown to limit eGFR decline and LVMI increase, as compared to conservative monitoring.[218] Although no studies have compared different antihypertensive regimens in children and adolescents with ADPKD, the Work Group agreed that blockade of RAS with ACEi or ARB is the preferred approach for management of BP in this group. These medications are widely utilized, with good efficacy and a reassuring side-effect profile in many children and adolescents with high BP, proteinuria, and/or glomerular hyperfiltration, including those with ADPKD.[218,841–844]

Certainty of evidence. The grade of certainty of evidence for choice of antihypertensive in children and adolescents with ADPKD was very low, due to the sparseness of evidence.

Values and preferences. Limiting the rate of progression to kidney failure and other complications of ADPKD is critically important to people with ADPKD. Earlier intervention (i.e., in childhood) has been proposed to be of particular benefit to long-term clinical outcomes in ADPKD. Moreover, ACEi or ARBs have been used widely 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 is not intrusive in routine clinical practice. Given these considerations, the Work Group, therefore, surmised that despite the very-low grade of certainty of trial evidence specific to children with ADPKD, most, if not all, people with ADPKD, and parents and/or guardians of children with ADPKD, would choose to utilize ACEi or ARBs in the appropriate clinical setting. No current evidence supports 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 the following: 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 them in liquid form.

Consideration for implementation. ACEi or ARB can cause hypotension, hyperkalemia, and an increased SCr level, in addition to other established side effects. Therefore, a reasonable approach is to periodically monitor BP, electrolytes, and kidney function in young people receiving these medications. The risk of an acute decrease in eGFR is of particular concern in people with renal artery stenosis or an eGFR <30 ml/min per 1.73 m^2. These medications can cause adverse developmental effects in the fetus and should be avoided during pregnancy. Parents and/or guardians and female patients (as developmentally appropriate) should be counseled regarding this risk. Such medications should be provided by prescribers who have 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 are low in cost. Therefore, if antihypertensive therapy is needed to control high BP in children and young people with ADPKD, the Work Group recommends RASi as a first-line pharmacologic therapy.

Practice Point 9.2.7: 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.

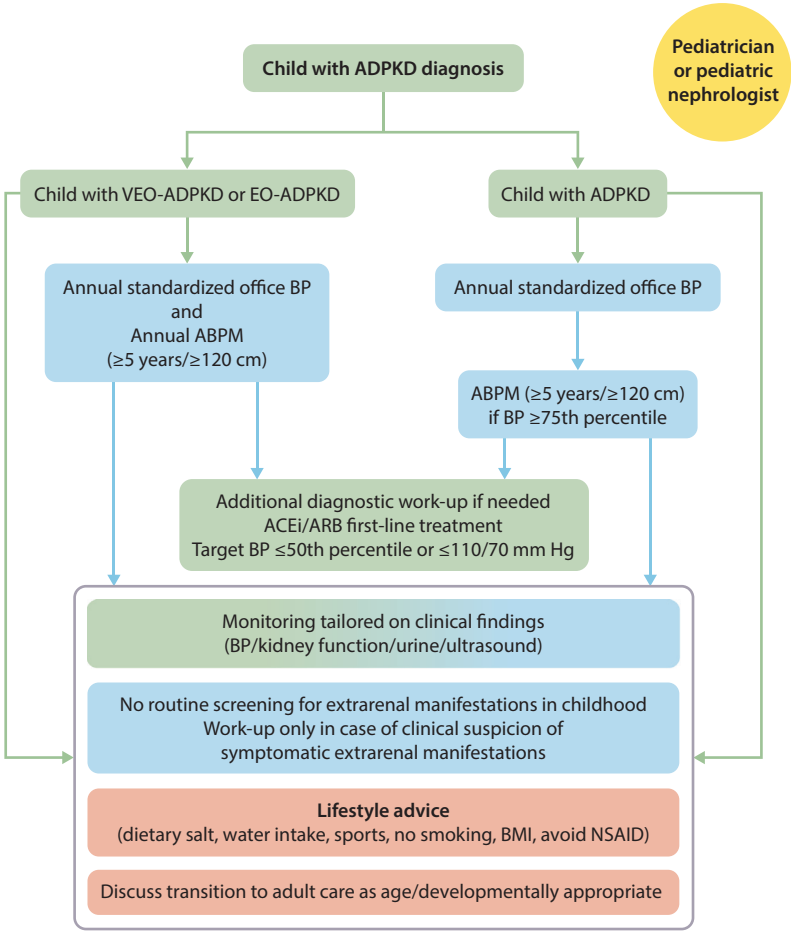


Figure 52 | Follow-up of children with autosomal dominant polycystic kidney disease (ADPKD), which should be performed by a pediatrician or pediatric nephrologist. ABPM, ambulatory blood pressure monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; EO, early onset; NSAID, nonsteroidal anti-inflammatory drug; VEO, very early onset.

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, the degree of BP control, and laboratory (e.g., kidney function, electrolytes, urinalysis for hematuria and/or 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.[845]

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

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

Hepatic cysts are observed in <4% of children with ADPKD, with no cases of significant liver disease having been described.[802,815,828] The prevalence of pancreas or spleen cysts in children with ADPKD is not known, but it is believed to be less common than in 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*), HNF1B nephropathy, or in the cases of concerning symptoms.

Although earlier studies suggested that the risk is higher for cardiac valve disease in children with ADPKD,[44] more recent studies have shown a low frequency of such disease.[218,647,846] Therefore, screening for cardiac valvular disease should be pursued in only cases in which a cardiac

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

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

UTIs are a common cause of fever in children. Studies have reported an increased incidence of UTIs for children with ADPKD,[460,801,828,847] but concerns of potential bias have been raised.[460] No reports have been made of increased incidence of severe UTIs in children with ADPKD. Thus, general principles of UTI diagnosis and treatment apply, including urinalysis, urine culture, possibly blood tests, and ultrasound.[848–850] Treatment of UTI should follow local recommendations per 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.[460] 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., being unresponsive to standard treatment or having an untypically severe clinical presentation).

Abdominal pain is common, affecting 10%–20% of both children with ADPKD[460,801,847] and otherwise healthy children. Symptomatic kidney cyst complication is rare in children with ADPKD, but imaging occasionally reveals incidental kidney cyst hemorrhage (i.e., in the absence of pain). Thus, in most cases, the etiology of abdominal pain in children with ADPKD mirrors that of otherwise healthy children, and standard management should be pursued. If kidney cyst complication is suspected as a cause of abdominal pain, abdominal MRI (or CT) may help to clarify the picture. Frequent use of NSAIDs should be avoided, due to the underlying kidney disease, and multidisciplinary treatment of chronic pain also should be initiated early in children and adolescents.[460]

Clinical evaluation of suspected nephrolithiasis should be performed in the same way as it is in healthy children, including an analysis to look for hypocitraturia. Ultrasound is the preferred imaging modality to look for kidney stones.

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

The prevalence of proteinuria was 20% in children with ADPKD, in a recent meta-analysis.[829] Concerns have been raised that this finding may have been influenced by a selection bias in the documenting centers. However, proteinuria is an established and treatable risk factor for progression of CKD in children.[834,851] ACEi and ARBs are recommended for treating proteinuria in children with CKD.[215] The same principles apply for evaluation and treatment of proteinuria in ADPKD as apply 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.

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.[435,828] No data are available on particular risks associated with desmopressin treatment, but given the known effects of vasopressin 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 and in children with enuresis and ADPKD.[460,852]

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.

Although isolated kidney cysts are rare in children,[825] the studies on incidence and prevalence were mainly performed in the 1980s and 1990s.[460] 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.*[853]

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 (Figures 52 and 53).

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

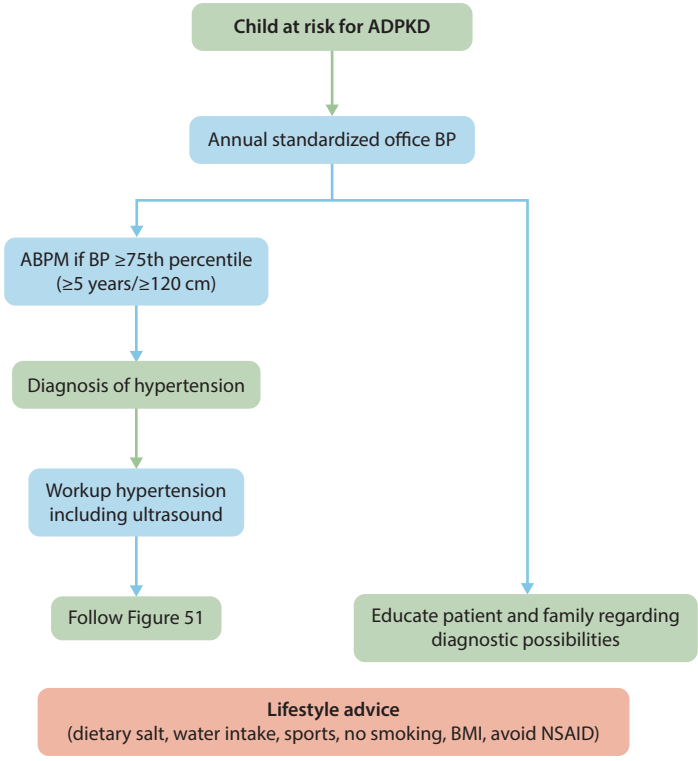


Figure 53 | Follow-up of children at risk for autosomal dominant polycystic kidney disease (ADPKD), which can be performed by a general practitioner, pediatrician, or pediatric nephrologist. ABPM, ambulatory blood pressure monitoring; BMI, body mass index; BP, blood pressure; NSAID, nonsteroidal anti-inflammatory drug.

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.[140,686] No studies have 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.[854,855] Furthermore, a high BMI and obesity have been linked with the occurrence of CKD, hypertension, and the development of metabolic syndrome.[845,856] A healthy lifestyle with regular exercise, avoidance of smoking, avoidance of nephrotoxic drugs, and a healthy diet with appropriate caloric and fluid intake should be advised from the early stages of ADPKD, and a normal BMI should be promoted from childhood.[818,845]

The growing child should not be on diets that include a low protein intake or caloric restriction for management of ADPKD. Children with ADPKD should follow general recommendations for a healthy diet, consistent with WHO guidelines, and should maintain a healthy body weight.[692] Children with ADPKD and hypertension or CKD should follow a diet in accordance with the guidelines for all children with hypertension or CKD.[215,857] Children and guardians should be aware that cyst bleeding associated with contact sports rarely occurs, but it is more likely in the setting of nephromegaly. If a particular sport or physical activity repeatedly is followed by gross hematuria, then 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. Assessment for extrarenal manifestations should be recommended as stated in Chapter 6.

Recommendations for the transition process from pediatric to adult care have been published for children affected by kidney disease, including collaborative guidelines from the International Society of Nephrology (ISN)/International Pediatric Nephrology Association (IPNA).[858,859] Although most of the studies in people with CKD about transition of care have been conducted in a kidney-transplant setting,[860] encouraging reports have been made of structured and successful transition programs in non-transplant settings as well.[861] The importance of a planned transition for those affected by ADPKD and other cystic kidney disease is becoming increasingly apparent.[862] National descriptions of pediatric-to-adult transition experiences, systems, and pathways further reinforce these observations and the importance of multidisciplinary constructs within these programs.[863,864] As no standard or consensus approach to the transition from pediatric to adult nephrology has been established, the transition should be individualized to the particular patient, family, and clinical settings (Figure 54).

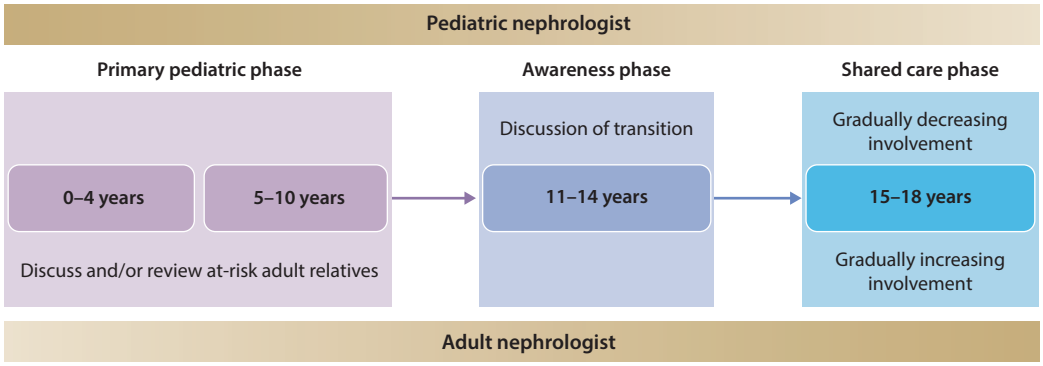


Figure 54| Suggested transition scheme for autosomal dominant polycystic kidney disease (ADPKD).

At this important clinical-care juncture, family planning and extrarenal manifestations take on increased importance (Chapters 6 and 8). In addition, as ADPKD is a relatively common and slowly progressive disease, children transitioning into adult care do not necessarily need to be managed at a specialized ADPKD center. However, caregivers are encouraged to maintain knowledge of active research studies and novel therapies to support optimal care and research-study participation of young adults with ADPKD. This process 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.

Questions asked of nephrologists by people with ADPKD do not infrequently include queries regarding how they might discuss ADPKD with their children or grandchildren.[747,821] The Work Group believes that such discussions present an opportunity to empower people with ADPKD and their families to openly discuss the condition in a manner that they feel is appropriate, given their situation or scenario.[755] Furthermore, a support for affected parents and grandparents is to share their experiences with others, for both personal and potential family benefits. An appropriate approach may be to provide information directly and/or to refer people to ADPKD centers of expertise that can provide advice, if indicated. In some situations, including a pediatric nephrologist in the discussion, if possible, may be appropriate, along with anticipating some broad areas of concern, such as diagnostic methods, treatment, complications, and prognostication. Although no 2 clinical scenarios in this setting will be exactly alike, adopting an open approach that does not engender fear or alarm, but rather in an informative and supportive manner, is important.

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.

Insufficient evidence exists to support the use of any targeted or disease-modifying treatments for ADPKD, including use of tolvaptan, in affected children at this time,[810,865,866] though a single RCT has indicated tolerability of tolvaptan and suggests a potential effect on annual TKV expansion.[387] A trial of curcumin did not show benefit in children affected by ADPKD.[867] However, a single trial on pravastatin use in children and young adults resulted in a significantly slower increase in htTKV over time, as compared to that with placebo.[457] Further trials are required. Specific trials in children also are required before the benefit identified in adults can be expected to extend definitively to affected children in certain scenarios. Children and families, if they are eligible, might consider enrolling in ADPKD clinical trials. Even though few new ADPKD trials are 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, although nuanced situations may occur in which individualized consideration within local approval or access pathways may 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, is also needed.
- 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 in rapid progression of ADPKD in childhood.
- Studies are needed to examine the impact of additional genetic variants on the prognosis for children with ADPKD.

- Studies are needed to assess the impact of early and aggressive treatment of hypertension during childhood on ADPKD disease progression at a later age.
- Studies are needed to assess the impact of high-normal (75th–95th percentile) BP on kidney and CVD risk in children with ADPKD.
- 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 of statin use for TKV growth in children.
- Research is needed to assess which group of children with ADPKD include the best candidates for clinical trials.
- Studies are needed to assess the updated and validated consensus approach(es) to a 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 requires expertise from various medical specialties. People presenting with the disease will usually need to see a range of specialized healthcare 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 approach to management of people with ADPKD proposed below is based on evidence from the care of people with other complex, syndromic, and/or genetic conditions. No evidence indicates 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 in which healthcare providers and patients share the best available evidence, and people are supported in considering options and making informed decisions (Figure 55). This collaborative process may deal with care that people need straightaway, or care needed in the future, such as through advance care planning (Appendix 2). The process involves choosing tests and treatments based both on evidence and people's individual preferences, beliefs, and values. Thus, people should understand, via discussion and information-sharing, the risks, benefits, and possible consequences of the various available options. 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 making no change to what they are currently doing.[868,869]

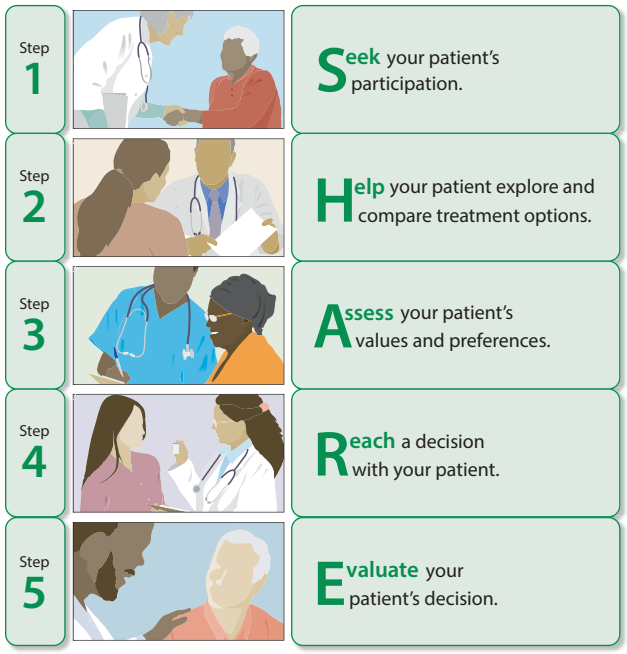


Figure 55 | The SHARE approach for shared decision-making. Reproduced from The SHARE Approach: A Model for Shared Decision-making—fact sheet accessed at https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/factsheet.html.

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 that are used to standardize care, reduce variation, equalize access, improve quality of care, and maximize patient outcomes in a specific population.[870,871] Care pathways are used to interpret guidelines and other recommendations for local, regional, and national implementation, and they account for care transitions (e.g., from pediatric to adult care, or early CKD to KRT or conservative care). The implementation of such pathways needs to include consideration of patient preferences, 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., nonkidney as well as kidney manifestations, including mental health considerations), as well as all research perspectives (Figure 56). Holistic care 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, centers of excellence, or healthcare reference centers in some jurisdictions) may optimize monitoring and treatment of extrarenal complications.[872] Shared decision-making with primary care physicians, or co-management 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 a person for specialist advice will depend on the individual person. The composition of the multidisciplinary care team needs to be adjusted to the (extra)renal manifestations of the disease, which vary widely from person to person, and the severity of CKD, which may determine the goals of specific therapies.

In settings in which access to medical care is limited by resources or location, new technologies, such as telehealth,

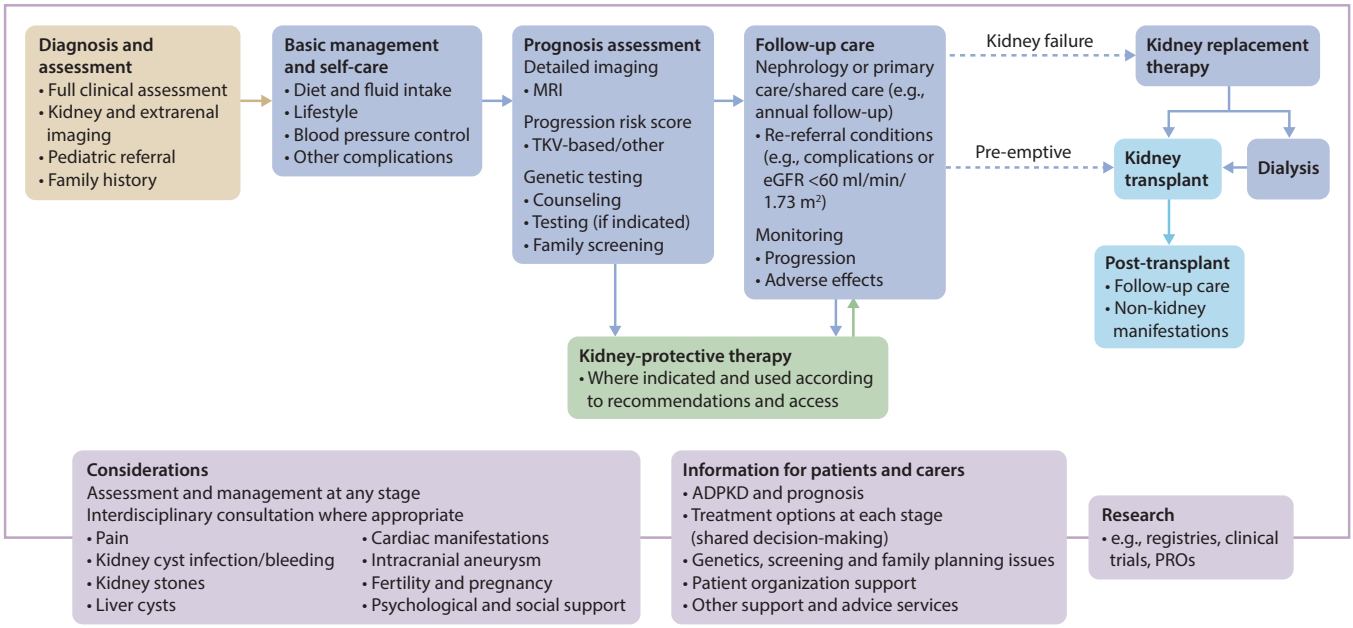


Figure 56| A proposed autosomal dominant polycystic kidney disease (ADPKD) care pathway. Ultrasound-based kidney imaging, including kidney length measurements, could be considered if MRI or computed tomography is not routinely available. eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PROs, patient-reported outcomes; TKV, total kidney volume. Adapted from EAF Co-chairs *et al.*[766]; Mao *et al.*[874]; Ong *et al.*[875]

should be considered. A systematic review concluded that eHealth self-management interventions have the potential to improve disease management and health outcomes in CKD[873]; however, barriers remain, and more research is needed in ADPKD.

For a detailed discussion of prognostic assessment in ADPKD, please refer to Chapter 1.

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 is enabling and facilitating active participation of people with ADPKD. Thus far, the evidence base for decision-making about most clinical interventions in ADPKD has a low or very low grade of certainty, reflecting the lack of sufficiently powered studies. Historically, trials in ADPKD have adopted a disparate array of outcome measures.[876] Initiatives such as the SONG-PKD study are establishing a codesigned set of outcomes with involvement of all stakeholder groups.[877] In addition, emerging and patient-centered measures for key outcomes, such as pain, are critical to the success of future trials.[233] Given the array of emerging trial opportunities, collaborative and innovative clinical trial designs (e.g., platform trial approaches) should be considered, to optimize the ability of people with ADPKD to participate, along with delivering cumulative research efficiency and expedited outcomes.[878,879] The incorporation of such trial approaches with patient registries and cohort studies additionally will 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 and should have relevant literacy.

The availability of genetic testing for people with ADPKD is increasing, with established diagnostic and prognostic values (see Chapters 1 and 8). 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, means that ensuring that nephrologists and other healthcare providers have relevant literacy in terms of genetics and genetic testing is necessary.[880] 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 a 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 that cause multisystemic complications, the care pathways in ADPKD may be complex and may need to involve care coordination or multiple care providers.[881] Although the majority of people with ADPKD present in adulthood, the need for coordination can be especially challenging at stages of healthcare transition. Care coordinators or patient navigators can be any healthcare or

social care provider, or a patient organization commissioned for that purpose. In most people with ADPKD, the nephrologist oversees the nephrology and the overall care. The patient and nephrologist may benefit from the assistance of care coordination (or patient navigation), helping to facilitate what are sometimes stressful and costly interactions with other care providers.[882] Specific support for people with ADPKD in the workplace, through a discussion between the person, the physician, and the employer, could help keep them engaged in full-time employment throughout the patient journey.[883]

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.

Self-management by patients of their chronic disease increasingly is being viewed as essential to improving health behaviors, health outcomes, and QoL.[884] Self-management education programs empower patients and improve adherence by emphasizing the role of patient education in preventive and therapeutic healthcare activities. They usually consist of organized learning experiences designed to facilitate adoption of health-promoting behaviors. Such programs usually are separate from clinical patient care, but they often are run in collaboration with healthcare providers.[885] The principles of effective self-management are summarized in Figure 57.

Self-management is now considered a specific component in the optimal care model in CKD,[237] and it may help reduce CKD progression and prevent complications.[886] Also, evidence from the Chronic Disease Self-Management Program (CDSMP) indicates that, in some conditions, such as diabetes, self-management has been proven to be effective for reducing healthcare utilization and the societal cost burden.[884]

Practice Point 10.7: Healthcare systems should promote the participation of people with ADPKD in registries that 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, the Polycystic Kidney Disease (PKD) Outcomes Consortium, and the U.S. PKD Foundation.[887] The SDTM allows for electronic submission to regulatory agencies.

Examples of established ADPKD-specific registries include the following:

- ADPedKD: https://www.adpedkd.org/index.php?id=about (pediatric);
- ERKReg (ERKNET): https://www.erknet.org/patients-registry/registry-mission;
- PKD Foundation: https://connect.pkdcure.org/adpkd-registry/; and
- UK RaDaR: https://ukkidney.org/rare-renal/metadata (adults and pediatric).

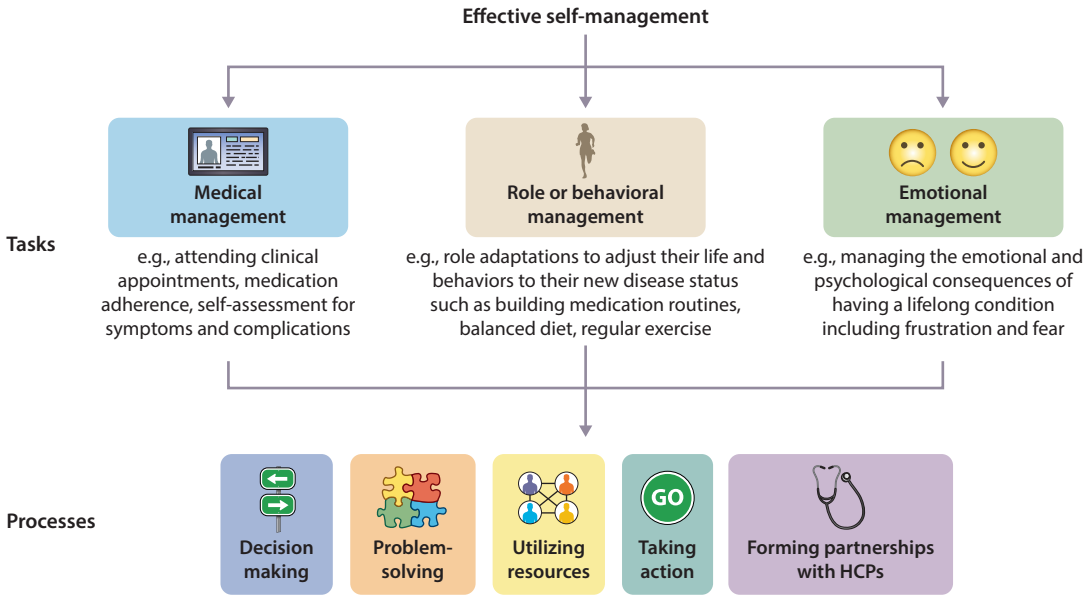


Figure 57 | Principles of effective self-management. Please refer to Chapter 7 for more details on lifestyle and psychosocial care of people with autosomal dominant polycystic kidney disease. HCPs, healthcare providers. Reproduced from Lightfoot *et al.*[886]

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

Patient-support activities that could be targeted to the appropriate stage and interest of the audience include the following:

- 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 healthcare providers or patient-leaders;
- participation in mutual patient-support groups, especially through peer support, to allow people to have a greater understanding of day-to-day living with ADPKD;
- 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 the design and development of studies and clinical trials; and
- 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 of such promotion are campaigning for reimbursement coverage for treatments, improved healthcare provisions, and legal provisions to avoid discrimination for families with a genetic disease (e.g., regarding insurability). Patient organizations can be helpful in encouraging people to get more care, earlier.

Patient organizations should also interact with healthcare providers, academia, industry, government, and regulatory agencies to promote research, ensure the patient voice and/or experience is reflected in all aspects of clinical and experimental research, including the development of new treatments and trial designs, and provide input to health-technology assessments.[5]

Patient organizations exist in multiple countries. A partial list may be found at: https://www.pkdinternational.org/index.php/membership.

Research recommendations

- Determine the cost effectiveness of multidisciplinary care pathways or multidisciplinary team approaches for people with ADPKD, including assessing the availability of a care coordinator.
- Determine how multidisciplinary care pathways could best function in settings with low or middle levels of resources.
- Investigate the role of telehealth in delivering ADPKD care, particularly in settings with low and middle levels of resources 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–healthcare provider communications.
- Investigate whether and which models of self-management in ADPKD are cost-effective.
- Evaluate specific patient-reported outcome measures as a component of routine clinical care and audit.
- Increase the representation of people from diverse ethnic backgrounds, including non-Caucasians, in future clinical research populations, recognizing the potential for undetected ethnic or racial differences in clinical presentation, prognosis, or treatment response.
- Refine widely used diagnostic codes (International Classification of Diseases, revision 10 [ICD-10]; Orphanet nomenclature of rare diseases [ORPHA]; Systemized Nomenclature of Medicine—Clinical Terms [SNOMED]) for ADPKD and its associated features, and their matching tables, to improve case identification for clinical care and research.

Methods for guideline development

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

This guideline adhered to international best practices for guideline development (Supplementary Tables S2–S4),[888,889] and has been reported in accordance with the Institute of Medicine and Appraisal of Guidelines for Research & Evaluation (AGREE) II reporting checklists.[890] The processes undertaken for the development of the *KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease* are as follows:

- appointing Work Group members and the ERT;
- finalizing guideline development methodology;
- defining the 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 as appropriate;
- grading the 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 grade of 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; and
- finalizing and publishing the guideline.

Commissioning of the Work Group and ERT for the guideline. 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 to serve 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 of the certainty of the evidence per outcome, and grading of the overall certainty of the evidence for the recommendations.

Defining the scope and formulating key clinical questions. The guideline Work Group, with assistance from the ERT, defined the overall scope and the goals of the guideline, and drafted a preliminary list of topics and key clinical questions. This process included making a determination about which topics the ERT would address via systematic review. Issues that were considered when determining topics to be systematically reviewed included the following: the specificity of the topic to ADPKD (e.g., tolvaptan treatment vs. prevention of kidney stones or management of dialysis); the importance of the topic to the majority of patients, families, and healthcare providers; prioritization of medications and imaging interventions; the likelihood that sufficient evidence exists to inform recommendations; time requirements; and available ERT resources.

Details of the PICOD questions are provided, with prioritized outcomes noted in Table 22. Outcome prioritization was based primarily on the SONG-PKD study outcome set.[877] We translated the SONG-PKD study outcome categorization into the structure proposed by Grading of Recommendations Assessment, Development and Evaluation (GRADE).[891] The SONG-PKD study "core" outcomes preliminarily were considered to be characterized as one of the following: of "critical" importance (GRADE rating 7–9); a "middle-tier" outcome, considered to be "important but not critical" (GRADE rating 4–6); or an "outer-tier" outcome, 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 study categorization. Of note, several outcomes of interest to the Work Group were not addressed by the SONG-PKD study, including harms (adverse events), nonspecific pain, liver-related outcomes, and dialysis-related outcomes. Several

Table 22 | Clinical questions and SR topics in PICOD format

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
Chapter 1. Nomenclature, diagnosis, prognosis, and prevalence					
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, MIC, PKD consortium, ADPKD Outcomes Model, other models ◦ *NOT models that predict effectiveness of treatment (e.g., TEMPO 3:4)* • Genetic markers • PKD1-T, PKD1-NT (hypomorphic vs. fully penetrating), PKD2, others ◦ *NOT polymorphisms, SNPs, non-PKD genetic factors.* • htTKV (or TKV), any imaging technique • Other imaging findings (e.g., cyst count, texture) • Laboratory tests/biomarkers • eGFR (indexed for age) • Urine biomarkers (e.g., crystalluria, urine/plasma urea ratios, tubular biomarkers, albuminuria) • Plasma biomarkers (e.g., glycemia, copeptin, lipid profile, bicarbonate, uric acid) • Global omics (e.g., proteomics, RNA) • FGF23 • Combinations of tests • Urinary tract/cyst infection • Prevalent diabetes • Obesity/BMI		• **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 22 | (Continued)

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
		• Family history of ADPKD (age at kidney failure) • Pediatric studies: Any predictor (including BP pattern)			
How do the estimates of htTKV as measured by different imaging techniques compare as predictors of progression of kidney disease?	ADPKD	htTKV	Alternate imaging technique CT MRI Ultrasound, including 3D vs. conventional	• **Progression of kidney disease** • Change in kidney function (GFR, eGFR, SCr doubling, GFR slope, etc.) • Change in CKD severity • Incident kidney failure • Change in htTKV or TKV	Longitudinal ≥1 yr f/up N ≥ 30
How do non-TKV measures on imaging compare with htTKV or add as predictors of progression of kidney disease?	ADPKD	• Cyst count • Kidney length • Other imaging measures from CT, MRI, ultrasound	htTKV	• **Progression of kidney disease** • Change in kidney function (GFR, eGFR, SCr doubling, GFR slope, etc.) • Change in CKD severity • Incident kidney failure • Change in htTKV 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* sub-group: known ICA • Subgroup by age	BP target	Alternate BP target	• **BP** • **CKD progression (by GFR)** • **Ruptured ICA** • **Death** • **AEs, serious attributable** • Left ventricular hypertrophy • PKD progression (by TKV)	Longitudinal ≥1 yr f/up Comparative N ≥10/group For AE: Single group N ≥ 30
What are the comparative effectiveness (benefits) and harms of different antihypertensive agents?	ADPKD (with high BP) • *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** • **AEs, serious attributable** • Left ventricular hypertrophy • PKD progression (by TKV)	RCT (or extension studies of RCTs) ≥1 yr f/up N ≥ 10/group For AE: Single group N ≥ 30
Chronic kidney pain					
How accurate are different imaging tests to diagnose kidney or liver cyst infections and how do the different imaging tests compare?	ADPKD with kidney or liver cyst infection	• PET • ^{111}In WBC • Gallium • MRI • CT • Ultrasound	Alternative imaging test Gold standard (aspiration)	• **Cyst infection**	Comparison with gold standard or alternative test N ≥10

(*Continued on following page*)

Table 22| (Continued) **Clinical questions and SR topics in PICOD format**

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
How do different antibiotics or duration of antibiotic treatment compare for treatment of kidney or liver cyst infections?	ADPKD with kidney or liver cyst infection	Antibiotic treatment	Different antibiotic (will record specific nature of antibiotic) Same treatment with alternate duration of treatment	• **Cure (infection clearance)** • **Recurrence** • **Harms**	RCT (or extension studies of RCTs) ≥1 yr f/up N ≥ 10/group For harms: Any longitudinal N ≥ 30
What pain or QoL scales have been validated in the ADPKD population?		• QoL scale • Pain measure	Alternative QoL or pain measure	• **Pain** • **QoL** • Progression • Workdays lost • Analgesia dose, type, etc.	Comparative Validation No sample size or follow-up duration limitations
RCC					
How does the risk of RCC compare between people with ADPKD and the general CKD population or general population?	ADPKD *A priori* subgroup: post-transplantation		General population or other people with CKD *A priori* subgroup: post-transplantation	• **Renal cell cancer incidence or prevalence** • Type of RCC	Registry (or other generalizable sample) N ≥ 100
Chapter 3. CKD management and progression, kidney failure, and kidney replacement therapy					
CKD management and progression					
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 mo f/up Comparative 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 mo f/up Comparative N ≥ 10/group

Table 22 | (Continued)

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
Kidney transplantation					
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)** • Surgical complications (CD III/IV) • Surgical complications: transfusions, any • Delayed graft function	Any duration Comparative N ≥ 10/group (no date exclusions)
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

(*Continued on following page*)

Table 22| (Continued) **Clinical questions and SR topics in PICOD format**

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
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]** • 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 Single group N ≥ 30 Exclude studies prior to 2013
Chapter 4. Therapies to delay the progression of kidney disease					
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, theine) restriction • Dietary acid restriction • Dietary bicarbonate/citrate supplementation • Caloric restriction (to maintain optimal body weight) • Increased water intake • β-hydroxybutyrate supplementation • Frequent small meals • Special diets ◦ Mediterranean ◦ DASH ◦ Vegetarian ◦ Low osmolar ◦ Ketogenic ◦ Intermittent fasting ◦ High fiber (or supplementation) • Smoking • Exercise • Other lifestyle	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 AEs	Longitudinal ≥1 yr f/up Comparative N ≥ 10/group For harms: Single group N ≥ 30

Table 22 | (Continued)

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
What are the comparative effects of pharmacologic interventions to slow ADPKD progression?	ADPKD	• V_2 receptor antagonist ◦ Tolvaptan ◦ Lixivaptan • Somatostatin analogues ◦ Octreotide ◦ Lanreotide ◦ Pasireotide • Tyrosine kinase inhibitor ◦ Tesevatinib • Glucosylceramide synthase inhibitor ◦ Venglustat • Nrf2 activator ◦ Bardoxolone • AMPK activator ◦ Metformin • CFTR inhibitor • Pioglitazone • Statins • 2-deoxy-D-glucose • Niacinamide • Hydralazine • SGLT2i • Anti-miR17 agents • Stem-cell based therapies • mTOR inhibitors *Exclude:* • *Bosutinib* • *HIF-PHI*	• No pharmacologic intervention (including placebo) • Alternative pharmacologic intervention	• **CKD progression (by GFR)** • **PKD progression (by TKV)** • **Liver size** • **Death** • **Pain** • **Harms: serious AEs** • **Harm: liver injury** • **QoL** • **Functional outcomes** • **Psychosocial outcomes** • Bulk symptoms • PKD complication: urinary tract infections • Side effect: Polyuria (tolvaptan) • Side effect: Serious thirst (tolvaptan) • Extrarenal manifestations • Harms, mild (mild hypoglycemia, nausea, vomiting, diarrhea, gallstones) • Harm: pulmonary, including. cough • Harm: discontinuation due to AEs	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. PLD					
What are the comparative effects of dietary or lifestyle interventions to slow liver cyst progression?	PLD, with or without ADPKD	• Dietary caffeine (xanthin, theine) restriction • Caloric restriction (to maintain optimal body weight) • β-hydroxybutyrate supplementation • Special diets ◦ Mediterranean ◦ DASH ◦ Vegetarian ◦ Low osmolar ◦ Ketogenic ◦ Intermittent fasting ◦ High fiber (or supplementation) • Lifestyle (exercise, weight control)	• No or alternative dietary intake or lifestyle intervention	• **Liver volume** • **Liver cyst volume** • **Bulk symptoms** • **Pain** • **Harms: serious AEs** • **QoL** • **Functional outcomes** • **Psychosocial outcomes** • Harms/AEs (diarrhea, bradycardia)	Longitudinal ≥1 yr f/up Comparative N ≥ 10/group

(*Continued on following page*)

Table 22| (Continued) **Clinical questions and SR topics in PICOD format**

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
What are the benefits and harms of hormone therapy on PLD?	PLD, with or without ADPKD	• Estrogens ◦ Estrogen-based oral contraception ◦ Other estrogen-based contraception ◦ Hormone (replacement) therapy • Progesterone • IVF hormonal therapy • Tamoxifen (and other selective estrogen receptor modulators) • Risk factors: history of, number of pregnancies	• No or alternative hormone interventions	• **Liver volume** • **Liver cyst volume** • **Bulk symptoms** • **Pain** • **Harms: serious AEs** • **QoL** • **Functional outcomes** • **Psychosocial outcomes** • Harms/AEs (diarrhea, bradycardia)	Longitudinal ≥1 yr f/up Comparative or single group N ≥ 10/group
What harms are associated with different routes of administration of hormone therapy in people with PLD?	PLD, with or without ADPKD	• Estrogens ◦ Estrogen-based oral contraception ◦ Other estrogen-based contraception ◦ Hormone (replacement) therapy • Progesterone • IVF hormonal therapy • Tamoxifen (and other selective estrogen receptor modulators) • Risk factors: history of, number of pregnancies	• Route of delivery (oral, IUD, etc.)	• **Liver volume** • **Liver cyst volume** • **Bulk symptoms** • **Pain** • **Harms: serious AEs** • **QoL** • **Functional outcomes** • **Psychosocial outcomes** • Harms/AEs (diarrhea, bradycardia)	Longitudinal ≥1 yr f/up Comparative or single group N ≥ 10/group
What are the effects of pharmacologic interventions to slow PLD progression?	PLD, with or without ADPKD	• Somatostatin analogues ◦ Octreotide ◦ Lanreotide ◦ Pasireotide • Ursodeoxycholic acid • mTOR inhibitors	• No or alternative pharmacologic intervention	• **Liver volume** • **Liver cyst volume** • **Bulk symptoms** • **Pain** • **Harms: serious AEs** • **QoL** • **Functional outcomes** • **Psychosocial outcomes** • Harms/AEs (diarrhea, bradycardia)	RCT (or extension studies of RCTs) ≥1 yr f/up N ≥ 10/group For harms: Any longitudinal N ≥ 30
What are the effects of invasive procedures or surgery to manage liver or kidney cysts or pain?	ADPKD or PLD, with or without ADPKD	• Cyst aspiration • Cyst drainage • Cyst sclerosis • Embolization (transarterial) • Fenestration • Liver resection • Liver transplantation • Nerve blocks • Denervation • Other invasive pain management	• No or alternative invasive intervention	• **Pain** • **Kidney/liver size** • **Cyst volume** • **Surgical complication: CD V (death)** • **Bulk symptoms** • **QoL** • Functional outcomes • Psychosocial outcomes • Surgical complications: serious, various	Any duration Comparative N ≥ 10/group For harms: Single group N ≥ 30

Table 22| (Continued)

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
What are the benefits and harms of percutaneous drainage to treat liver cyst infections?	PLD, with or without ADPKD, with cyst infection	Percutaneous drainage	No drainage	• **Cure (infection clearance)** • Harms	Any duration Comparative N ≥ 10/group For harms: Single group N ≥30
Chapter 6. ICAs and other extrarenal manifestations					
What is the prevalence of ICA and the incidence of ruptured ICA in ADPKD?	ADPKD	(None)	(None)	• **ICA prevalence** • **Ruptured ICA incidence**	Nationally representative population samples (or equivalent) Take temporal effects and imaging techniques into account
What is the risk of ICA rupture in people with ADPKD versus in the general population?	General population, either total population or people with no known ICA	ADPKD	No ADPKD	• **Ruptured ICA/SAH**	Comparative Comparative N ≥ 30/group Take temporal effects and imaging techniques into account
What are the predictors for prevalent ICA or rupture of ICA?	ADPKD	• Any • Modifiable risk factors ◦ Smoking ◦ BP control ◦ Treatment • Nonmodifiable risk factors ◦ Family history ◦ Genetics ◦ Sex ◦ Age • Known aneurysm (or no known aneurysm), for risk of ICA rupture (overlap with imaging) • Location and number of previous aneurysms • Previous treated aneurysms • Previous ruptured aneurysms		• **ICA** • **ICA rupture**	Predictor analysis • Comparison of with vs. without risk factor N ≥ 30 Take temporal effects and imaging techniques into account
What are the benefits and harms of imaging people with ADPKD for ICA?	ADPKD	Imaging for ICA	• No screening • No comparator • Alternate imaging strategy (including timing of repeat tests)	• Death • ICA rupture • Stroke • Intervention complication • Psychosocial outcomes • QoL • Functional outcomes	Longitudinal ≥1 yr f/up N ≥ 30 or N ≥ 10 with post-imaging intervention (e.g., surgical clipping) (if total N < 30) Take temporal effects and imaging techniques into account

(*Continued on following page*)

Table 22 | (Continued) **Clinical questions and SR topics in PICOD format**

Clinical question	Population	Intervention/predictor	Comparator	Outcomes[a]	Design
Chapter 7. Lifestyle and psychosocial aspects					
• No systematic reviews conducted for clinical questions addressed this chapter					
Chapter 8. Pregnancy and 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 (Where available, data from systematic reviews conducted for earlier chapters are cited.)					
Chapter 10. Approaches to the management of people with ADPKD					
• No systematic reviews conducted for clinical questions addressed this chapter					

ADPKD, autosomal dominant polycystic kidney disease; AE, adverse events; AMP, adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; ANOVA, analysis of variance; 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 inhibitor; htTKV, height-adjusted total kidney volume; ICA, intracranial aneurysm; IUD, intrauterine device; IVF, *in vitro* fertilization; MIC, Mayo Imaging Classification; 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; PICOD, population, intervention, comparator, outcomes, and study design; PKD, polycystic kidney disease; PLD, polycystic liver disease; PROPKD, Predicting Renal Outcomes in ADPKD; QoL, quality of life; RCC, renal cell carcinoma; RCT, randomized controlled trial; SAH, subarachnoid hemorrhage; SCr, serum creatinine; SGLT2i, sodium-glucose cotransporter-2 inhibitors; SNP, single nucleotide polymorphisms; SR, systematic review; T, truncating; TEMPO 3:4, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume; V_2, vasopressin-2; yr f/up: year(s) follow-up; ^{111}In WBC, indium-labeled white blood cells.
[a]Bold outcomes are critical; unbolded outcomes are important.

SONG-PKD study outcomes were translated to match outcomes of interest to the Work Group (e.g., depression was translated to psychosocial and/or mental health outcomes; fatigue and impact on family and/or friends was translated to QoL). After the addition of outcomes that were not included in the SONG-PKD study, the outcomes were organized preliminarily according to the SONG-PKD study tiers (core outcomes, middle-tier, outer-tier). The Work Group and Co-Chairs completed surveys based on the GRADE system of prioritizing importance by ranking it from 1 (least important) to 9 (most critical). The ERT then assisted the Co-Chairs in determining the final level of prioritization for each topic. Outcomes that were determined to be either critical, or important but not critical, were included in evidence profiles.

All evidence reviews were conducted in accordance with the *Cochrane Handbook for Systematic Review of Interventions*,[892] and the Agency for HealthCare Research and Quality *Evidence-based Practice Center Program Methods Guide*.[893] Guideline development adhered to the standards of the GRADE system.[894]

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, with an update during the public review on October 10, 2023. The search strategies for all databases are provided in Supplementary Table 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 their relevance and gain consensus among reviewers, the entire team screened and achieved consensus on a series of initial batches, each of 100 abstracts. Potentially relevant citations were retrieved in full-text form. These articles were rescreened in duplicate. Disagreement about inclusion was resolved by discussion with the entire team.

The search identified 10,099 citations (Figure 58). Including 22 additional records suggested by Work Group members, 1013 were screened in full-text form, and 238 records were extracted and summarized—74 for Chapter 1, 29 for Chapter 2, 36 for Chapter 3, 60 for Chapter 4, 21 for Chapter 5, and 18 for Chapter 6.

Data extraction. Data extraction was performed by one ERT member. Extracted data from each study were reviewed by another ERT member to confirm their accuracy. The ERT designed a form to capture data on the 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/.

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 (those that evaluated comparisons of interest).[895] 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 (those 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.[896] Specifically, for comparative studies, we evaluated whether the cohorts were comparable and whether the study accounted for potential confounders.

For all studies, including single-group (noncomparative) studies, we determined the following: whether the types of analyses used were intention-to-treat (or otherwise included all participants) or per-protocol (or other incomplete assessment); whether selection of participants into the study was based on participant characteristics observed after the start of intervention; use of selective reporting; and whether the reporting was clear, without discrepancies, and with 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 they were subject to other potential biases or methodological problems of note. In cases in which methodological issues may have pertained to only some reported outcomes, this point was noted.

For each study, assessment of risk of bias was done by one of the reviewers, and 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 for cases in which 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 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 what constituted sufficient similarities. We did not exclude meta-analyses solely because of statistical heterogeneity (differences across studies in effect-size estimates). We conducted restricted maximum-likelihood model meta-analyses of the OR for outcomes, using Stata software (StataCorp).

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots showing standardized mean-effect sizes and risk ratios, and by χ^2 tests. A P value < 0.05 was used to denote statistical heterogeneity, and an I^2 was

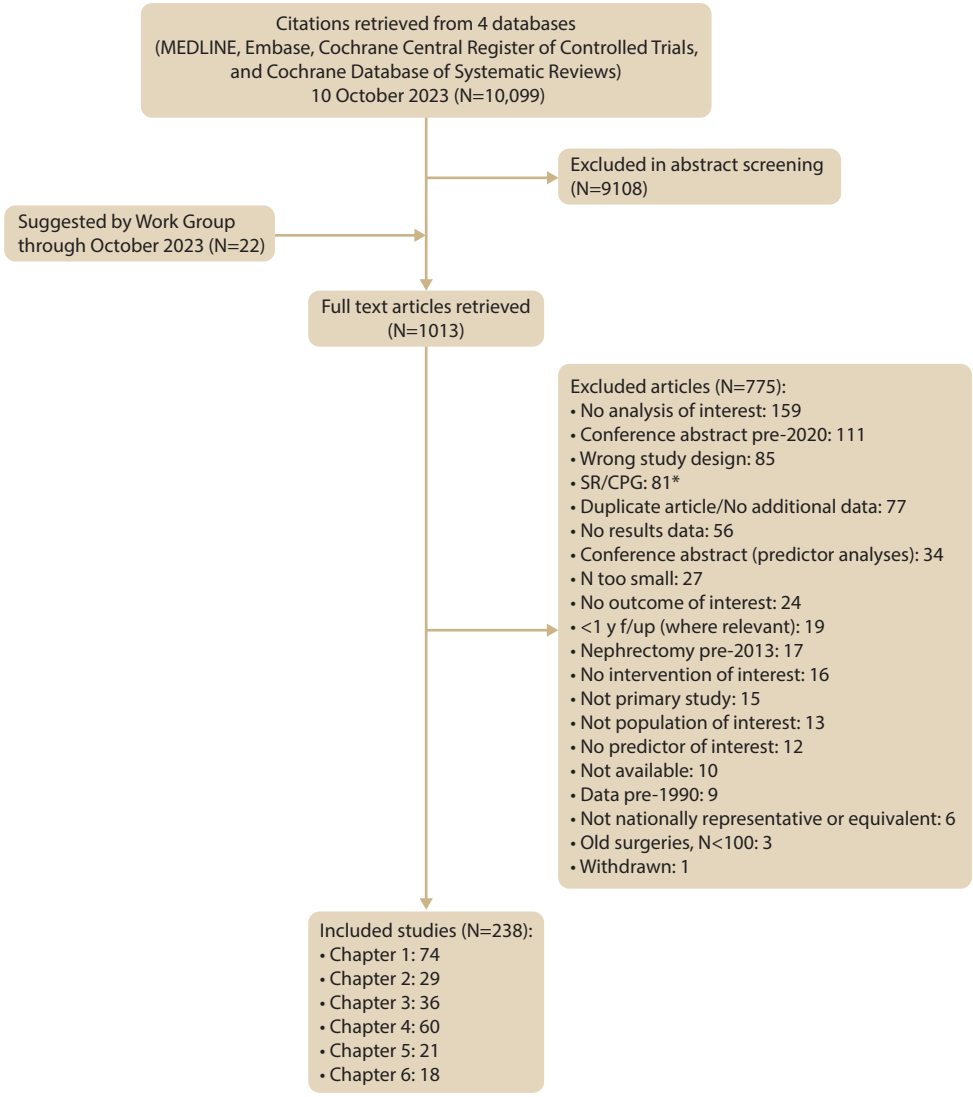


Figure 58 | Literature flow diagram. f/up, follow-up. *Reference lists from existing systematic reviews (SR) and clinical practice guidelines (CPG) screened. No additional (missed) studies added.

calculated to measure the proportion of total variation in the estimates of treatment effect that resulted from heterogeneity beyond that due to chance.

Grading the certainty of the evidence. *Evidence profiles.* Evidence profiles were developed to include a description of the population and the intervention and comparator. In addition, the evidence profiles include a 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 evidence profiles 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 23),[894] which is a method to grade the certainty of the evidence for each outcome. For each outcome, the potential grade for the certainty of evidence for each intervention–outcome pair was started as being "high" but then was lowered if any of the following were true: the methodological certainty of the aggregate of studies had serious limitations; important inconsistencies were present in the results across studies; uncertainty remained about the directness of evidence (including limited applicability of the findings to the population of interest); the outcome-measure estimates were imprecise or were based on few studies; or the likelihood of reporting bias was considered to be high. The final grade for the certainty of the evidence for an outcome was high, moderate, low, or very low (Table 23).

Grading the strength of the recommendations. The strength of a recommendation was graded as either "Level 1" or "Level 2" (Table 24). The strength of a recommendation was determined by the following aspects: 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 25).

Table 23 | GRADE system for grading the certainty of evidence

Study design	Step 1—starting grade for the certainty of the evidence	Step 2—lower the grade	Step 3—raise the grade for observational studies
RCT	High	Study limitations: −1, serious −2, very serious	Strength of association +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose–response gradient
Observational	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious −3, extremely serious	
		Publication bias: −1, strongly suspected	

GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial.

Table 24 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade	Patients	Clinicians	Policy
Level 1, "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	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.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

KDIGO, Kidney Disease: Improving Global Outcomes.

Table 25 | Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	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.
Certainty of evidence	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.
Values and preferences	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.
Resource use and costs	The higher the cost of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

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.

The overall certainty of the evidence. This factor 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 given a grade of A, B, C, or D (Table 26).

Patient values and preferences. The Work Group included 3 people living with ADPKD. These members' unique perspectives and lived experiences, 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 into the treatment-

Table 26| Classification for the grade of the certainty of evidence

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

management pathway, were considered in the grading of 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., family and caregiver time); and changes in productivity. No formal economic evaluations, including cost-effectiveness analyses, were conducted.

Developing the recommendations. The guideline statements were developed by the Co-Chairs and members of the Work Group. Recommendations were developed during in-person meetings (Berlin, Germany, June 2022; 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 the feedback, the guideline was further revised by the Work Group, as appropriate. All Work Group members provided input on the 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 healthcare providers better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they 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"; Level 2, "we suggest") and the certainty of the evidence (A, B, C, D). Each recommendation statement is followed by a Key Information section (*Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, Considerations for implementation*), and the rationale for the recommendation. Each recommendation is linked to relevant evidence profiles. 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 that specifically address 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. The 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 that were known to domain experts and were missed by the electronic literature searches were added to the group of retrieved articles and reviewed by the Work Group.

The ERT did not systematically review all topics, including—as noted in Table 22—the following: lifestyle and psychosocial interventions (other than selected dietary interventions); interventions specifically related to pregnancy and reproduction; interventions related to 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 a higher minimum sample size, 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.

Biographic and disclosure information

Olivier Devuyst, MD, PhD (Work Group Co-Chair), graduated from UCLouvain in Brussels (Belgium) and trained at the Technion Institute (Haifa, Israel) and at the Johns Hopkins Medical School (Baltimore, Maryland, USA). He is Full Professor of Medicine at the University of Zurich (Zurich, Switzerland) and the UCLouvain Medical School, with a joint appointment at Saint-Luc Academic Hospital in Brussels.

Dr. Devuyst and his group use a multilevel approach to investigate the genetic architecture of kidney diseases. This joint work identified new mechanisms involved in rare genetic disorders affecting tubular cells, paving the way for novel therapeutic approaches. In parallel, the team demonstrated the crucial role of water channels (aquaporins) in peritoneal dialysis, and he developed preclinical strategies to improve the efficiency of dialysis.

Dr. Devuyst has authored more than 450 articles that have been cited more than 50,000 times (h-index 101). He is funded by national and international agencies, including the European Union (EU) and the National Institutes of Health (NIH). He served as president and as a board member of the Belgian and Swiss societies of nephrology, coordinated several EU-funded research networks, and established the Working Group on Inherited Kidney Disorders of the ERA. He co-chairs the university priority program on rare diseases in Zurich and is the coordinator of the Institute for Rare Diseases at Saint-Luc Academic Hospital in Brussels.

Dr. Devuyst has been the laureate of several international prizes, including the 2022 Chan Woon Cheung Visiting Professor of the Hong Kong Society of Nephrology, the 2019 D.G. Oreopoulos Award of the Canadian Society of Nephrology, and the 2019 ERA-EDTA Award for Outstanding Basic Science Contributions to Nephrology. He is Associate Editor of *Kidney International*, *Nephrology Dialysis Transplantation*, and *Orphanet Journal of Rare Diseases*; and he serves on the Editorial Board of *Clinical Journal of the American Society of Nephrology*, *Peritoneal Dialysis International*, *Frontiers in Physiology,* and *Pflügers Archiv: European Journal of Physiology.*

OD reports receiving consultancy fees from Otsuka Pharmaceutical, Sanofi*, and Vertex Pharmaceuticals*; and serving on advisory boards for Galapagos* and Otsuka Pharmaceutical.**

**Monies paid to institution.*

Vicente E. Torres, MD, PhD (Work Group Co-Chair), received MD and doctoral degrees from the University of Barcelona, and moved to the Mayo Clinic (Rochester, Minnesota, USA) in 1972 for research and clinical training. He joined the faculty in 1979, and became Professor of Medicine in 1991, and the Robert M. and Billie Kelley Pirnie Professor of Kidney Research in 2018. Polycystic kidney disease has been the focus of his research. Dr. Torres was the principal investigator for the NIH-funded CRISP observational study and for the HALT-PKD clinical trial, and industry-funded clinical trials of vasopressin V_2 receptor antagonists (TEMPO 3:4 and REPRISE). He served as Chair of the Division of Nephrology and Hypertension at the Mayo Clinic, Director of the NIH-funded Mayo Kidney Disease Research Training Grant, Director of the Robert M. and Billie J. Pirnie Mayo Translational PKD Center, and on the Scientific Advisory Board of the PKD Foundation and NIH study sections. He also co-chaired the KDIGO Controversies Conference and the 2017 Federation of American Societies for Experimental Biology (FASEB) Science Research Conference on PKD. His contributions to research were recognized by the 2007 Lillian Jean Kaplan International Prize for Advancement in the Understanding of PKD and the 2019 John P. Peters Award of the American Society of Nephrology.

VET reports receiving consultancy fees from Janssen Pharmaceuticals, Mironid*, Palladio Biosciences*, and Vertex Pharmaceuticals*; and research support from Blueprint Medicines*, Mironid*, Palladio Biosciences*, Reata Pharmaceuticals*, Regulus Therapeutics*, Sanofi*, and Tribune Therapeutics.**

**Monies paid to institution.*

Curie Ahn, MD, PhD, is a nephrologist from Seoul, Korea. In 2000, she started conducting xenotransplantation research in Korea and has contributed to the advancement of this field over the past 20 years. She served as the President of the Korea Xenotransplantation Association (June 2013–May 2021) and as a councilor of the International Xenotransplantation Association (2015–2019). As a clinical research scientist, she has established the national cohort for CKD (KNOW-CKD),

ADPKD, and for organ transplantation (Korean Organ Transplantation Registry [KOTRY]) to provide a basis for translational research.

Currently, Dr. Ahn is the General Secretary of the Asian Society of Transplantation as well as a Councilor of The Transplantation Society, with the goal of improving transplantation medicine, especially in Asia. In addition, as the immediate past director of VitalLink Academy, she has been actively participating in clinical capacity-building in deceased organ transplantation in many Asian countries during the past 15 years.

CA declared no competing interests.

Thijs R.M. Barten, MD, PhD, is a researcher from Radboudumc, Nijmegen, the Netherlands. He received his medical training at Radboud University (Nijmegen, the Netherlands), after which he completed his PhD in the Department of Gastroenterology and Hepatology of Radboudumc. His research focused on clinical guidance for polycystic liver disease, including participating in the European Association for the Study of the Liver (EASL) guideline on management of cystic liver diseases.

TRMB declared no competing interests.

Godela Brosnahan, MD, PhD, FASN, is a Professor of Medicine at the University of Colorado. She completed medical school at the University of Würzburg, in Würzburg, Germany, with a dissertation, in July 1983. Her residency and fellowship training led to her board certification in internal medicine (1990) and nephrology (1991). She moved to Denver, Colorado, USA in 1992 to embark on a clinical research fellowship in ADPKD under the supervision of Dr. Patricia Gabow, where she met her future husband. To continue her clinical work and research, she had to repeat a residency and fellowship training in the U.S. After this interruption, she resumed clinical investigations in ADPKD, while also serving as a busy clinician and teacher at the University of Colorado (Denver, Colorado, USA) and, from 2006–2010, at the University of Arkansas for Medical Sciences (Little Rock, Arkansas, USA), where she served as director of a very successful nephrology fellowship training program. In 2010, she was called back to the University of Colorado to oversee the HALT-PKD trials and continue with additional clinical studies in ADPKD. She was promoted to Professor of Medicine at the University of Colorado, and retired from active clinical duties in July 2022.

GB declared no competing interests.

Melissa A. Cadnapaphornchai, MD, is Professor of Pediatrics at Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, in Philadelphia, Pennsylvania, USA. She received her medical degree from the University of Michigan (Ann Arbor, Michigan, USA). She trained in pediatrics at the University of Colorado (Boulder, Colorado, USA) and in pediatric nephrology at the University of Virginia (Charlottesville, Virginia, USA) and the University of Colorado. She served as the director of pediatric research for the University of Colorado PKD Research Group for over a decade. Her clinical research has helped to define the natural course of ADPKD in childhood, as well as the clinical features and risk associated with very-early-onset ADPKD and hypertension in children with ADPKD. She conducted the first 2 interventional trials in children and young adults with ADPKD, examining the impact of BP control with angiotensin-converting enzyme inhibition, and the effect of pravastatin treatment on progression of both kidney and cardiovascular disease. Dr. Cadnapaphornchai also participated in the recent European clinical trial of tolvaptan in children with ADPKD. She has written over 70 articles and 10 book chapters and was a member of the Network for Early Onset Cystic Kidney Disease Consensus Group, which published guidelines for the diagnosis and management of children with ADPKD in 2019.

MAC reports receiving consultancy fees from Otsuka Pharmaceutical.

Arlene B. Chapman, MD, is Chief of Nephrology at the University of Chicago (Chicago, Illinois, USA). She has been funded continuously by the NIH and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for over 30 years, focusing on clinical manifestations of ADPKD, and imaging biomarkers and treatment for hypertension and progressive kidney disease. Dr. Chapman served on the steering committee for the HALT PKD trials, as well as for the TEMPO 3:4 and REPRISE trials. She has over 240 publications to her credit, and she mentors undergraduate and graduate students, as well as physician scientists.

ABC reports receiving research support from NIDDK, Otsuka Pharmaceutical, Regulus Therapeutics, and UpToDate; and speaker honoraria from the Cleveland Clinic, the National Kidney Foundation, and the Renal Physicians Association.

Emilie Cornec-Le Gall, MD, PhD, FERA, is a Professor of Nephrology at the University of Brest and Brest University Hospital (Brest, France), a member of the L'Institut national de la santé et de la recherche médicale (INSERM) UMR1078, and the coordinator of the Brest National Center of Expertise in Rare Kidney Diseases (MARHEA). She earned her medical degree, a specialization in nephrology, and her PhD in genetics from the University of Brest. She completed her postdoctoral fellowship in Prof. Peter Harris's lab at the PKD Translational Research Center at Mayo Clinic (Rochester, Minnesota, USA).

Dr. Cornec-Le Gall has published over 60 manuscripts. Her research, particularly in the Genkyst cohort—an observational cohort of ADPKD patients from 28 centers in western France initiated in 2011 by Prof. Y. Le Meur—has highlighted the importance of variant types in ADPKD disease severity and prognostication. She has contributed to the identification and clinical characterization of several atypical forms of ADPKD associated with variants in new cystic genes.

In 2016, she received the Stanley Shaldon Award for Young Investigators from the ERA. She is currently the co-chair of the Genes and Kidney Working Group of the ERA.

ECLG declared no competing interests.

Joost P.H. Drenth, MD, PhD, FRCP, is the professor of Hepatology at the Department of Gastroenterology and Hepatology of the Amsterdam University Medical Center, Amsterdam, the Netherlands. Dr. Drenth received his medical degree (1990) from Maastricht University (Maastricht, the Netherlands) and was trained as a gastroenterologist at the Radboud University Medical Center (Nijmegen, the Netherlands). He obtained his PhD in 1996 with honors for the study of a rare autoinflammatory syndrome known as hyper-IgD syndrome. He served as head of the Department of Gastroenterology and Hepatology (2010–2023) and established a prolific research agenda in rare inherited liver diseases. During his scientific career, he discovered genes for autoinflammatory diseases, inherited pancreatitis, and polycystic liver disease. He initiated over 50 rigorous clinical trials in many rare diseases, such as hereditary angiodysplasias, autoimmune disorders, polycystic liver disease, and polycystic kidney disease, among others. This research opened the pathway to novel treatment options for rare disease patients. Professor Drenth was a research fellow at the National Institutes of Health, Bethesda, Maryland, USA (2002–2004), and he became a Fellow of the Royal College of Physicians, London, UK, in 2016, and a member of the Academia Europaea in 2017. Dr. Drenth has authored over 600 peer-reviewed papers, and he is the current Editor-in-Chief of the *United European Gastroenterology (UEG) Journal* and serves as Vice President (2024) of the UEG.

JPHD reports receiving consultancy fees from Camurus; and research support from Camurus* and Gilead Sciences.**
**Monies paid to institution.*

Ron T. Gansevoort, MD, PhD, FERA, FASN, is Professor of Medicine and a nephrologist at the University Medical Center Groningen (UMCG), in Groningen, the Netherlands. Professor Gansevoort's work has been instrumental in the development of the novel global definition and classification of CKD, the development of novel endpoints for clinical trials in the field of nephrology, and the first registered treatment for ADPKD. He is committed to attracting greater attention for screening for early CKD and prevention of progressive kidney function loss at a general population level, and specifically in patients with ADPKD. At his institution, he established the Polycystic Kidney Disease Center, which has been acknowledged as an (inter)national center of expertise by the Dutch and EU authorities.

Professor Gansevoort has coauthored over 700 peer-reviewed manuscripts (h-index 101). He is/was member of the steering committee of several large-scale consortia (CKD-Prognosis Consortium, DIPAK, European Renal Association COVID-19 Database [ERACODA], Dutch Renal Patients COVID-19 Vaccination [RECOVAC], Check@Home), and clinical trials in the field of CKD (Dutch Renal Patients COVID-19 Vaccination [ARTS-DN], the Study on the Safety of the Drug Runcaciguat and How Well it Works When Given at the Highest Dose as Tolerated by Individual Patient Whose Kidneys Are Not Working Properly and Suffering at the Same Time From High Blood Sugar and/or High Blood Pressure and a Disease of the Heart and the Blood Vessels [CONCORD], Renal Lifecycle), and polycystic kidney disease (TEMPO 3:4, REPRISE, DIPAK-1, Study to Assess Glucosylceramide Synthase Inhibitor Efficacy in ADPKD [STAGED-PKD], An Exploratory, Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of Orally Administered GLPG2737 for 52 Weeks, Followed by an Open-label Extension Period of 52 Weeks in Subjects with Autosomal Dominant Polycystic Kidney Disease [MANGROVE]).

RTG reports receiving consultancy fees from AstraZeneca, Bayer Healthcare Pharmaceuticals*, Dutch Heart Foundation*, Dutch Kidney Foundation*, Galapagos*, GlaxoSmithKline*, Happitech*, Health Holland*, Ipsen*,*

Mironid, Otsuka Pharmaceutical*, Roche*, and Sanofi-Genzyme*; and research support from AstraZeneca*, Bayer Healthcare Pharmaceuticals*, Dutch Heart Foundation*, Dutch Kidney Foundation*, Galapagos*, GlaxoSmithKline*, Happitech*, Health Holland*, Ipsen*, Mironid*, Otsuka Pharmaceutical*, Roche* and Sanofi-Genzyme*. In addition, RTG reports owning the rights for the Orphan Medicinal Product Designation status for lanreotide. *Monies paid to institution.*

Peter C. Harris, PhD, is a consultant in the Division of Nephrology and Hypertension in the Department of Internal Medicine at Mayo Clinic in Rochester, Minnesota, USA, with a joint appointment in the Department of Biochemistry and Molecular Biology. Dr. Harris is Director of the Mayo Clinic Translational Polycystic Kidney Disease Center and Vice Chair of the Department of Biochemistry and Molecular Biology. He joined the staff of Mayo Clinic in 1999 and holds the academic rank of Professor of Medicine and Biochemistry/Molecular Biology, Mayo Clinic College of Medicine and Science. In 2024, Dr. Harris was recognized with the distinction of the Gordon H. and Violet Bartels Professorship in Cellular Biology. Dr. Harris' research laboratory focuses on genetic diseases of the kidney, especially PKD. Dr. Harris' research group previously identified the major gene for common ADPKD and the gene for ARPKD. More recently, they identified 2 genes for syndromic PKD, Meckel syndrome (MKS), and 3 minor ADPKD-like genes. In 2003, he received the inaugural Lillian Jean Kaplan Prize for Advancement in the Understanding of PKD, and in 2008, the Homer Smith Award from the American Society of Nephrology.

PCH reports receiving consultancy fees from Caraway Therapeutics, Janssen Pharmaceuticals*, Maze Therapeutics*, Mitobridge*, Otsuka Pharmaceutical*, PYC Therapeutics*, Regulus Therapeutics*, Renasant Bio*, Sentynl Therapeutics*, and Vertex Pharmaceuticals*; and research support from Acceleron Pharma*, Espervita Therapeutics*, Jemincare*, Merck*, and Regulus Therapeutics.**

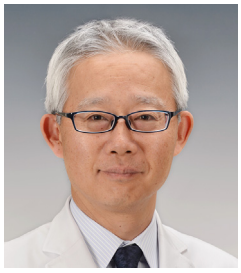
**Monies paid to institution.*

Tess Harris, MA, FCIM, was the Chief Executive of PKD Charity UK from 2012 until her death. As an individual with ADPKD who had received a kidney transplant and undergone dialysis and a nephrectomy, she was a tireless advocate for advancing the care of people with PKD by fostering close collaborations and dialogue among healthcare providers, researchers, and individuals with PKD, raising disease awareness, and improving education regarding PKD. Fueled by a personal connection to the disease, Tess demonstrated an unparalleled commitment to driving innovation and progress in the quest for effective treatments and improved quality of life for all people affected by PKD. Through her work at PKD Charity UK, she expanded outreach to the 70,000 persons affected by the disease in the UK, and made available a patient helpline that offers accessible information to educate those affected by PKD, and help alleviate the fear and isolation they may experience.

Tess shared her perspective as a PKD patient representative by serving on numerous PKD research initiatives, including, but not limited to, SONG (Standardised Outcomes in Nephrology), the PKD Outcomes Consortium, the International Research Advisory Committee of CanSOLVE CKD, UK Renal Registry, UK Kidney Research Consortium, and the European Patient Advocacy Groups of the European Reference Networks. Tess participated in a multitude of consulting activities related to PKD research, including the Pragmatic Randomised Trial of High or Standard Phosphate Targets in End-stage Kidney Disease (PHOSPHATE); Survival Improvement with Cholecalciferol in Patients on Dialysis (SIMPLIFIED) Registry; and Autosomal Dominant Polycystic Kidney Disease, or ADPKD, Advancement of Disease-modifying therapies through a European consortium (ADVANTAGE) trials; provided input on the NICE guidelines; and participated in an expert European Medicines Agency working group reviewing the use of total kidney volume as a prognostic marker together with patient age and eGFR.

Tess's dedication is further exemplified by her continuing pioneering efforts on the conception, development, and implementation of a groundbreaking PKD app in 2022. She was also instrumental in establishing the newly formed PKD Research Resource Consortium, aimed at boosting research and development in the PKD field. Additionally, she was a vital contributor to the first global ADPKD clinical practice guideline by KDIGO, showcasing her unwavering commitment to standardizing ADPKD care. Her courage and optimism inspired others to see that international partnerships among scientists, regulatory organizations, and patients are achievable and can enhance care in both the PKD community and the broader kidney disease community.

TH declared no competing interests.



Shigeo Horie, MD, PhD, is a urologist and professor in Japan, recognized for his clinical and research work on ADPKD. He graduated from the University of Tokyo's Faculty of Medicine, and then trained in nephrology at UT Southwestern Medical Center in Dallas, Texas, USA as a research and clinical fellow. In

2003, he became a professor and chairman of the Department of Urology at Teikyo University in Tokyo. In 2012, he assumed the same roles at Juntendo University, Graduate School of Medicine in Tokyo. He also holds endowed chairs in Advanced Informatics for Genetic Disease and Digital Therapeutics. Dr. Horie developed and analyzed *PKD1* mutant mice and has actively contributed to the development of new medicines for ADPKD. He chaired the committee on genetic kidney disease for the Ministry of Health and Welfare and organized Japan's clinical guidelines for ADPKD. He currently serves as the President of the Polycystic Foundation in Japan.

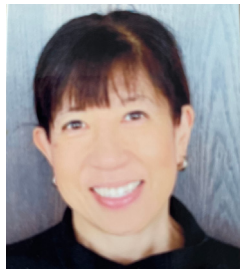
SH reports serving as a board member of Kyowa Kirin, Sanofi, and Welcia Holdings; receiving research support from Otsuka Pharmaceutical; and serving on the endowment department of Otsuka Pharmaceutical.*

**Monies paid to institution.*

Max C. Liebau, MD, is a Professor of Pediatrics, and a board-certified clinical consultant pediatric nephrologist and transplant physician at the Department of Pediatrics at the University Hospital Cologne, in Cologne, Germany, where he holds positions as Head of the Social Pediatric Center for Chronically Ill Children and Coordinator of Outpatient Service, as well as Head of Translational Pediatric Nephrology. Dr. Liebau combines his clinical training with his experience in cellular and molecular biology obtained in the Nephrology Research Laboratories in Freiburg and Cologne, Germany, and at the University of California, Santa Barbara, California, USA. His group follows a translational research approach to study pediatric genetic kidney diseases. Dr. Liebau initiated the international ARPKD registry study ARegPKD and is a coinitiator of the pediatric ADPKD registry study, ADPedKD. He has received multiple national and international awards, including the prestigious Adalbert Czerny Award. Research in the Liebau group is funded by the German Research Foundation, the EU Horizon program, the European Joint Program on Rare Diseases (EJPRD), and the German Federal Ministry of Education and Research, among others. Dr. Liebau currently serves as chair of the Inherited Kidney Diseases working group of the European Society for Paediatric Nephrology, and as chair of the clinical study group of the German Society for Pediatric Nephrology.

*MCL reports serving on an advisory board for Otsuka Pharmaceutical.**

**Monies paid to institution.*



Michele Liew, MBBS (Monash), FRACP, PGDipAvMed (Otago), is an Australian medical practitioner who has been practicing aviation medicine in Hong Kong for over 20 years. Her involvement as a patient in this project occurred via her nephrologist Dr. Sydney Tang. She is grateful to have the opportunity to participate and to learn from the group of international healthcare professionals in this specialized field.

ML declared no competing interests.

Andrew J. Mallett, MBBS, MMed, PhD, FRCP, FASN, FRACP, is an adult nephrologist with a special interest in genetic kidney disease and nephrogenetics. Having been a Churchill Fellow previously, he is a current Queensland Health Advancing Clinical Research Fellow with a strongly emerging clinical and research profile in this field. Currently Professor of Medicine at James Cook University, North Queensland, Australia and Clinical Fellow at the Institute of Molecular Biology at University of Queensland, Brisbane, Australia. Professor Mallett is also the National Director of the KidGen Collaborative at Murdoch Children's Research Institute, Melbourne, Australia, and Director of Clinical Research and a nephrologist at Townsville University Hospital, Douglas, Queensland, Australia. He is committed to improving the understanding of inherited kidney disease, as well as the clinical care and outcomes of Australians affected by it.

AJM reports receiving research support from Medical Research Future Fund, National Health and Medical Research Council*, PKD Australia*, and Sanofi-Genzyme*; serving on an advisory board for the Australian and New Zealand Society of Nephrology (unpaid), and GlaxoSmithKline (unpaid); serving as a site principal investigator for Dicerna Pharmaceuticals*, Reata Pharmaceuticals*, and Sanofi-Genzyme*; and receiving travel expenses from Otsuka Pharmaceutical.*

**Monies paid to institution.*

Changlin Mei, MD, is a renowned nephrologist and scientist. He is Professor of Internal Medicine at Shanghai Changzheng Hospital (Jing'an District, Shanghai, China), an affiliated teaching hospital of the Second Military Medical University. He served as Chairman of the Department of Nephrology at Changzheng Hospital and was the Founding Director of its Kidney Institute. He was a member of the Standing Committee of the Chinese Nephrology Association, as well as its Secretary and Vice President, and Chairman of the Shanghai Society of

Nephrology (SSN). He also served as the editor-in-chief and on standing committees for 10 national magazines.

Dr. Mei received his MD degree from the Second Military Medical University. He was a visiting scholar with Dr. Richard Tanner at the University of Southern California, 1993–1995, and Dr. Stefan Somlo at Yale University School of Medicine, 2000–2001. His pioneering research in the molecular mechanisms of renal fibrosis and polycystic kidney diseases, combined with over 40 years of clinical experience, have made him a revered key opinion leader in areas such as acute and chronic glomerulonephritis, nephrotic syndrome, acute kidney injury, blood purification, and cystic kidney disease.

Dr. Mei has won numerous awards and honors for his distinguished contribution to scientific research and clinical practice in nephrology. Under his leadership, the nephrology department has become a technology center, a research institute, and a key national study program. Dr. Mei has published more than 427 peer-reviewed papers, and 14 books; and he holds 6 patents.

CM declared no competing interests.

Djalila Mekahli, MD, PhD, is a pediatric nephrologist at the University Hospitals Leuven (Leuven, Belgium), professor in the faculty of Medicine and leader of the PKD research group in the Department of Cellular and Molecular Medicine at the Catholic University of Leuven (KU Leuven, Leuven, Belgium). Dr. Mekahli's research focuses on early stages of ADPKD, with the goal of identifying early biomarkers for ADPKD and unraveling the proximal molecular events that are essential in the progression of ADPKD. She leads a large and a well-characterized pediatric ADPKD clinic (with longitudinal clinical, imaging, and biorepositories database) and performs clinical research bridged to basic science. Her group published a novel imaging method (3D-ultrasound) which was used to develop "The Leuven classification of total kidney volume in ADPKD children" in collaboration with the CRISP consortium, constituting as a very big step in the research of pediatric ADPKD as it might be used in stratification of disease progression. Dr. Mekahli is the initiator and the principal investigator of ADPedKD, the global APDKD registry of children (www.adpedkd.org), in collaboration with several pediatric experts in the field. The ADPedKD registry is a web-based database, including both retrospective and prospective longitudinal data from young ADPKD patients, with currently almost 2000 children with ADPKD from all the continents enrolled. In addition, she is the co-chair of the workgroup for autosomal dominant structural kidney disorders (including ADPKD and tuberous sclerosis complex [TSC]) from the European Rare Kidney Disease Reference Network (ERKNet) and a board member of the European Kidney Health Alliance (EKHA).

DM reports receiving consultancy fees from Otsuka Pharmaceutical; and research support from Galapagos* and Otsuka Pharmaceutical.**
**Monies paid to institution.*

Dwight Odland is an ADPKD patient. He recently retired after a 30-year career in business development in the space industry, in which he led teams who won more than $1 billion in contracts. Dwight has been very active within the PKD community, acting as the Los Angeles Chapter Coordinator for the PKD Foundation since 2005, supporting 3 KDIGO conference teams and subsequent papers, and serving 2 terms (6 years) on the Board of the PKD Foundation during a time of growth in research, staff professionalism, and advocacy success.

Dwight has also assisted the PKD Foundation on projects such as PKD Connect Conference (PKDCON), the Registry, the Walk for PKD, and research grant reviews. He has also been a renal research grant reviewer for the Department of Defense Congressionally Directed Medical Research Program. Most importantly, he has personally met with and supported hundreds of PKD patients in their journeys.

As a patient advocate, Dwight has authored and co-authored several PKD-related papers for organizations such as KDIGO, Standardised Outcomes in Nephrology (SONG), and the University of Colorado. Dwight received a living donor transplant in August, 2023. Dwight earned his BS in Business Administration & Finance, *cum laude*, from California State University, Northridge. Currently, he lives in Simi Valley, California (USA), with Jean, his wife of 25 years. Dwight's favorite activities are traveling, skiing, hiking, and golfing.

DO reports receiving stock and stock options from Santa Barbara Nutrients, Inc.

Albert C.M. Ong, BM BCh, MA, DM, FRCP, FAoP, FERA, Professor of Renal Medicine at the University of Sheffield and Consultant Nephrologist at the Sheffield Kidney Insitute, Sheffield, UK. Born in Malaysia, he was educated at the University of Oxford, trained as a clinician–scientist at University College London and Oxford before taking up his present post. Work in his laboratory has focused on understanding the molecular basis of cyst formation, and the determinants of biological variation and drug discovery in ADPKD, for which he received the 2022 ISN Lillian Jean Kaplan International Prize. He is Co-Director of the Medical Research Council (MRC)-National Institute for Health and Care Research (NIHR) United Kingdom Renal Ciliopathies National

Network (CILIAREN) and leads specialist services for patients with inherited kidney diseases at the Sheffield Kidney Institute. He has published over 200 papers, trained over 30 postgraduate students and fellows, lectured globally, provided strategic leadership, and given expert testimony in the ADPKD field. He is a member of the ERA Council and served as Scientific Program Chair for the 61st ERA Congress in 2024.

ACMO reports receiving consultancy fees from Crinetics Pharmaceuticals, Galapagos*, GlaxoSmithKline*, Janssen Pharmaceuticals*, Ono Pharmaceutical*, and Vertex Pharmaceuticals*; serving on an advisory board for Mironid*; and serving on the steering committees for Palladio Biosciences* and Sanofi-Genzyme.**

**Monies paid to institution.*

Luiz F. Onuchic, MD, PhD, is Professor of Medicine at the University of São Paulo School of Medicine in São Paulo, Brazil. Dr. Onuchic received his medical degree from the School of Medicine and his PhD degree in renal physiology from the Institute of Biomedical Sciences, both at the University of São Paulo. He completed his medical residency training in internal medicine at the University of São Paulo Medical Center and his fellowship training in nephrology at the Johns Hopkins Hospital, Baltimore, Mayland, USA. He also received postdoctoral training in molecular pathogenesis of inherited nephropathies at Yale University, New Haven, Connecticut, USA, and at the Johns Hopkins University, Baltimore, Maryland, USA. Dr. Onuchic is the Chief of the Division of Molecular Medicine and the Head of the Laboratory of Cellular, Genetic and Molecular Nephrology at the University of São Paulo School of Medicine. He is a physician–scientist focused on the pathogenesis of polycystic kidney diseases and other genetic kidney disorders. He played a major role in the identification and characterization of the *PKHD1* gene, and using genetically modified mouse models orthologous to ADPKD, he has made key contributions to the elucidation of fundamental aspects of the pathogenesis of the ADPKD renal and cardiac phenotypes. Dr. Onuchic practices nephrology at the University of São Paulo Medical Center, where he is the Head of the Unit of Inherited Nephropathies. Additionally, he has been active in educating physicians and spreading knowledge about PKD over the past 25 years.

*LFO reports receiving consultancy fees from Otsuka Pharmaceutical; and serving on a steering committee for Palladio Biosciences.**

**Monies paid to institution.*

York P-C Pei, MSc, MD, FRCP(C), FACP, FASN, is a Professor of Medicine from the Division of Nephrology at the University of Toronto; a Senior Scientist from the Toronto General Research Institute; and the Director of the Centre for Innovative Management of Polycystic Kidney Disease, University Health Network in Toronto, Canada.

His research focuses on genetic, genomic, and translational research of hereditary kidney diseases with a major focus on ADPKD. He also made important contributions to genetic research of familial IgA nephropathy, familial nephrotic syndrome, and Alport syndrome. He has published over 180 peer-reviewed articles, collaborated widely with researchers nationally and internationally, and trained numerous clinical and research fellows in hereditary kidney disease.

He founded the Centre for Innovative Management for Polycystic Kidney Disease in 2016, which provides advanced diagnostic and novel therapeutics for ADPKD. More than 500 patients are currently followed or co-managed at the centre, with over 95% involved in at least one research project.

Dr. Pei was the co-recipient of the Lillian Jean Kaplan International Prize for Polycystic Kidney Disease in 2019, and the recipient of the Medal for Research Excellence by the Kidney Foundation of Canada in 2020.

YPCP reports serving on an advisory board for AbbVie-Calico, AstraZeneca, BridgeBio, GlaxoSmithKline, Maze Therapeutics, and Otsuka Pharmaceutical.

Ronald D. Perrone, MD, is Professor of Medicine and Distinguished Faculty at Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts, USA. He has had a wide-ranging interest in ADPKD, including basic investigations addressing mechanisms of ion transport by cystic epithelia, clinical investigations describing causes of mortality in the ADPKD kidney failure population, and participation and direction of clinical trials in ADPKD. He has participated in all of the U.S. interventional clinical trials in ADPKD, serving as the Boston site Principal Investigator and a member of the Steering Committees for the HALT-PKD study, the TEMPO 3:4 and REPRISE trials of tolvaptan in ADPKD, the Trial of Administration of Metformin in Polycystic Kidney Disease (TAME-PKD) study of metformin, and the Venglustat Study to Assess Glucosylceramide Synthase Inhibitor Efficacy in ADPKD (STAGED-PKD) study. He also served as site principal investigator for the tesevatinib (Kadmon) and bardoxolone (FALCON) studies. He initiated and co-led the PKD Outcomes Consortium and has been the principal individual

involved in bringing together the contributors from academia, the pharmaceutical industry, NIH, FDA, EMA, Clinical Data Interchange Standards Consortium (CDISC), and Critical Path Institute (C-Path). Total kidney volume was approved as a prognostic biomarker by both the FDA and the EMA as a result of these efforts. Dr. Perrone serves as Co-Director of the PKD Outcomes Consortium, the goal of which is to develop new approaches to achieving regulatory goals for ADPKD and ARPKD.

RDP reports receiving consultancy fees for AbbVie-Calico, Caraway Therapeutics, Janssen Pharmaceuticals*, Navitor Pharmaceuticals, Otsuka Pharmaceutical*, and Rex*; research support from Kadmon Corporation*, Palladio Biosciences*, Reata Pharmaceuticals*, and Sanofi-Genzyme*; serving as a Steering Committee member for Palladio Biosciences* and Sanofi-Genzyme*; and receiving fees from UpToDate.*

**Monies paid to institution.*

Gopala K. Rangan, MBBS, FRACP, PhD, MBA, MDiagGenomics, is Senior Staff Specialist in Renal Medicine and Transplantation at Westmead Hospital; Professor in Genetic Kidney Disease, University of Sydney; and Director of the Michael Stern Laboratory for Polycystic Kidney Disease at the Westmead Institute for Medical Research, in Sydney, Australia. As a clinician–scientist, Dr. Rangan's research goal is to develop effective treatments to prevent kidney failure and normalize healthspan in people suffering with ADPKD. He has published multiple translational papers on the molecular pathways in ADPKD, including vitamin D, cell cycle, nitric oxide, transcription factor, and DNA damage signalling. He led the multicenter Australian PREVENT-ADPKD trial, published in the *New England Journal of Medicine Evidence*, which provided the first high-quality evidence on the efficacy of increased water intake in ADPKD. He has led national/international consortia (Caring for Australians & New Zealanders with Kidney Impairment [CARI])-ADPKD, SONG-PKD, the retrospective epidemiologic study of Asian-Pacific patients with rapid disease progression of Autosomal Dominant Polycystic Kidney Disease [RAPID-ADPKD]) which established evidence-based clinical guidelines, consensus for clinical trial endpoints in ADPKD, and a multinational ADPKD network in the Asia-Pacific region. He is Chair of the Scientific Advisory Board of PKD Australia, and coestablished the Sydney Renal Genetics Network. Since 2013, he has mentored 23 postgraduate research students (most of whom are first or co-author on research publications) and trained 2 specialist PKD scientists.

GKR reports receiving research support from Danone Research, National Health and Medical Research Council of Australia*, Otsuka Australia Pharmaceutical*, and PKD Australia*; speaker honoraria from Otsuka Australia Pharmaceutical*; serving on the advisory board for Sanofi; serving on a scientific advisory board for PKD Australia; and receiving travel expenses from Asian Pacific Society of Nephrology.*

Brian Rayner, MBChB, FCP, MMED, PhD, is an emeritus Professor and Senior Scholar of the University of Cape Town (UCT), Cape Town, South Africa. He is past Head of the Division of Nephrology and Hypertension at the Groote Schuur Hospital and UCT, and he established the Kidney and Hypertension Research Unit in 2016. He is a past President of the Southern African Hypertension Society and is an executive member of the African Regional Advisory Group of the International Society of Hypertension. He graduated MBChB from UCT in 1978, received a Fellowship of the College of Physicians of South Africa (FCP) in 1986, and has a MMed and PhD from UCT. His doctoral thesis examined salt sensitivity and salt-sensitive hypertension in indigenous South African people. He received the World Hypertension League Award for Notable Achievement in Hypertension in 2014 for work related to his doctorate.

The Division of Nephrology and Hypertension and the Kidney and Hypertension Research Unit is an active training and research center training nephrologists from Sub-Saharan Africa, and it has active Masters and Doctoral programs. He developed protocols to guide treatment of various kidney diseases, including lupus nephritis, for use in the Division. In 2016, the International Society of Nephrology endorsed the Division as a Regional Training Centre of Excellence.

Dr. Rayner's active research interests are therapy of hypertension, mutations in the epithelial sodium channels (EnaC), genetic determinants of salt sensitivity and CKD, lupus nephritis, primary aldosteronism, assessment of adherence in hypertensive patients, physiological treatment of resistant hypertension, and genetics of severe hypertension in Blacks. Together with Professors Seedat and Veriava, they wrote the 2014 South African Hypertension Practice Guideline. He has served on the following guideline committees: WHO Pharmacological Treatment of Hypertension (2020); KDIGO ADPKD committee (current); and Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) Diabetes Guideline. He has authored 177 publications in peer-reviewed journals, has made over 120 presentations at local and international congresses, and has written 6 book chapters. He was/is a principal investigator and/or national principal investigator in the following trials: Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE); Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL); Dulaglutide Versus Insulin Glargine in Patients with Type 2 Diabetes and Moderate-to-Severe Chronic Kidney Disease (AWARD-7); Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein

Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE); Exenatide Once Weekly Plus Dapagliflozin Once Daily Versus Exenatide or Dapagliflozin Alone in Patients with Type 2 Diabetes Inadequately Controlled with Metformin Monotherapy (DURATION-8); REPRISE; Cardiovascular and Renal Microvascular Outcome Study with Linagliptin (CARMELINA); Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS); Study Assessing the Morbidity–Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease (SIGNIFY); Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD); Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD); Albuminuria-lowering Effect of Dapagliflozin Alone and in Combination with Saxagliptin And Effect of Dapagliflozin and Saxagliptin on Glycaemic Control in Patients with Type 2 Diabetes and Chronic Kidney Disease (DELIGHT); A Prospective, Multicenter Randomized Controlled Trial (PROTECTII); Anemia Studies in Chronic Kidney Disease: Erythropoiesis via a Novel Prolyl Hydroxylase Inhibitor Daprodustat–Non-Dialysis (ASCEND-ND); Evaluate Renal Function with Semaglutide Once Weekly (FLOW); A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with ISN/RPS 2003 Class III or IV Lupus Nephritis (REGENCY); A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Cardiovascular Disease, Chronic Kidney Disease and Inflammation (ZEUS); Research Study to Find Out How Semaglutide Works in the Kidneys Compared to Placebo, in People With Type 2 Diabetes and Chronic Kidney Disease (REMODEL); Zibotentan in Combination with Dapagliflozin Compared with Dapagliflozin in Patients with Chronic Kidney Disease (ZENITH-CKD); and A Research Study to See the Effects of CagriSema in People Living With Diseases in the Heart and Blood Vessels (REDEFINE); and other major international research studies.

BR reports serving on an advisory board for AstraZeneca, Bayer, Sanofi-Genzyme, and Servier; and receiving speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Cipla, Novartis, Sanofi-Genzyme, and Servier.

Roser Torra, MD, PhD, serves as the Chief of Clinical Nephrology and coordinates the Inherited Kidney Diseases (IKD) Clinic at the Nephrology Department of the Fundació Puigvert, Barcelona, Spain. She holds the position of Professor of Medicine at the Universitat Autònoma de Barcelona. She embarked on her journey in IKD in 1994 and completed her PhD on ADPKD in 1997. Since then, she has been deeply engaged in both clinical practice and research focusing on IKDs with over 200 national and international publications.

Professor Torra's involvement extends beyond research and clinical practice. She served as the European Representative in the Independent Data Monitoring Committee of the TEMPO 3:4 study. Presently, she actively participates in numerous trials and projects related to IKD, both nationally and internationally, while also supervising doctoral theses on these diseases. She also serves as a reviewer/advisor in this domain for various journals, meetings, project-evaluating agencies, and government policy-making bodies. Her expertise has been recognized in several KDIGO meetings. Professor Torra also serves as the site coordinator for the Spanish research network (RICORS2040), and for the ERKNet.

Professor Torra is President of the ERA from 2024 to 2027.

RT reports receiving consultancy fees from Otsuka Pharmaceutical; speaker honoraria from Otsuka Pharmaceutical; travel expenses from Otsuka Pharmaceutical; serving on an advisory board for the Independent Data Monitoring Committee, TEMPO 3:4 trial; and serving as current President of the ERA.

KDIGO Chairs

Michel Jadoul, MD, received his MD degree in 1983 at the Université Catholique de Louvain (UCLouvain), Brussels, Belgium. Dr. Jadoul trained in internal medicine and nephrology under the mentorship of Professor Charles van Ypersele de Strihou. He has served as chair at the Department of Nephrology of the Cliniques Universitaires Saint-Luc (2003–2023) and has been emeritus clinical professor at UCLouvain for a few months. Dr. Jadoul's current clinical activities focus on the follow-up of hemodialysis and CKD patients, and his main research interests have included β2-microglobulin amyloidosis, hepatitis C, and other complications (e.g., falls, bone fractures, sudden death) in hemodialysis patients, as well as cardiovascular complications after kidney transplantation and various causes of kidney disease (e.g., drug-induced).

Dr. Jadoul has coauthored over 360 scientific papers, most of them published in major nephrology journals. He is currently serving as an associate editor of *Nephrology Dialysis Transplantation*. In 2008, he received the International Distinguished Medal from the U.S. NKF. He was previously a member of the European Renal Association Council (2013–2016). Presently, Dr. Jadoul is a KDIGO Co-Chair.

MJ reports receiving consultancy fees from Astellas, AstraZeneca*, Bayer*, Boehringer Ingelheim*, Cardiorenal*, CSL Vifor*, GlaxoSmithKline*, Menarini*, Stada-Eurogenerics* and Vertex Pharmaceuticals*, research support from AstraZeneca*; speaker honoraria from AstraZeneca*, Bayer*, and Boehringer Ingelheim*; fees for expert testimony from Stada-Eurogenerics*; and travel support from AstraZeneca*.*
**Monies paid to institution.*

Morgan E. Grams, MD, PhD, MHS, is a nephrologist and PhD-trained epidemiologist. She is the Susan and Morris Mark Professor of Medicine at New York University, New York, New York, USA, where she helps lead the Division of Precision Medicine, a multidisciplinary computational research unit. Her research spans multiple areas of medicine, using multimodal data and advanced statistical methods to address clinically meaningful questions. She is the co-Principal Investigator of the CKD Prognosis Consortium (CKD-PC), a global consortium of over 250 investigators and 30 million patients. A graduate of Yale University for undergraduate training, Columbia University for medical school and residency, and Johns Hopkins University for nephrology fellowship and doctoral training, Dr. Grams has been honored with the Donald W. Seldin Young Investigator award from the American Society of Nephrology, the Garabed Eknoyan award from the National Kidney Foundation, several mentoring awards, and induction into the American Society of Clinical Investigation. She is the current Co-Chair of KDIGO.

MEG declared no competing interests.

Methods Representative

Reem A. Mustafa, MD, PhD, MPH, is a nephrologist with a master's degree in public health and a PhD degree in Health Research Methodology/Clinical Epidemiology. She is a Professor of Internal Medicine/Nephrology, University of Kansas Health System, and the Director of its Outcomes and Implementation Research Unit. Dr. Mustafa's area of research interest is the application of principles of evidence-based medicine in clinical and public health decision-making, with a focus on diagnosis. She also studies the effect of these principles on clinical and patient-important outcomes. Dr. Mustafa has extensive experience in the development and assessment of clinical practice guidelines through her work with The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. She has led multiple guideline development groups internationally, including with the World Health Organization (WHO), the Infectious Diseases Society of America (IDSA), the American Society of Hematology (ASH), and the Canadian Society of Nephrology (CSN). Dr. Mustafa is a member of the Executive Committee, and Chair of the Methods Committee, for the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. She is a cofounder of the U.S. GRADE network, and the Evidence Foundation, and she has published more than 300 peer-reviewed publications, with an overall Hirsch index of 78. She has been recognized by Clarivate, an analytics company, as one of the "true pioneers in their fields over the last decade demonstrated by the production of multiple highly-cited papers that rank in the top 1% by citations for field and year in the Web of Science."

RAM reports receiving consultancy fees from the World Health Organization and the Evidence Foundation; research support from the American College of Radiology, the American Society Hematology, Boehringer Ingelheim, and NIDDK; speaker honoraria from the Evidence Foundation and Institute for Clinical and Economic Review (ICER); and participating in an advisory board for the National Institutes of Health, on the board of directors for Evidence Foundation, and a medical advisory board for the National Kidney Foundation.

Evidence Review Team

Ethan M. Balk, MD, MPH, is associate director of the Center for Evidence Synthesis in Health (CESH) and professor at Brown University School of Public Health in Providence, Rhode Island, USA. He is project director of the Evidence Review Team (ERT) and has collaborated on numerous KDIGO guidelines, and prior to that, on Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines since 2000. As project director for this guideline, he provided methodological expertise in the guideline development process and led the collection, evaluation, grading, and synthesis of evidence and the revisions of the final evidence report. Dr. Balk also provided methodological guidance and training of Work Group members regarding topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research interests are evidence-based medicine, systematic review, clinical practice guideline development, and critical literature appraisal.

EMB declared no competing interests.

Craig E. Gordon, MD, MS, is Professor of Medicine at Tufts University Medical Center in Boston, Massachusetts, USA. Dr. Gordon graduated from New York University School of Medicine and received a master's degree in clinical care research from the Tufts University School of Graduate Biomedical Sciences. Dr. Gordon previously served as the assistant project director and associate director of the ERT for the 2020 KDIGO Clinical Practice Guideline for the Evaluation and Management of Candidates for Kidney Transplantation, and the 2018 and 2022 KDIGO Clinical Practice Guidelines for Hepatitis C in CKD, respectively.

Dr. Gordon provided methodological expertise to the Work Group during the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence for the guideline, as well as providing guidance to Work Group members in the areas of topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research and clinical interests are in the management of hepatitis C in patients with CKD, polycystic kidney disease, and thrombotic microangiopathies, as well as evidence-based medicine and systematic review related to other areas of nephrology.

CEG reported receiving consultancy fees from Alexion and Calliditas; research support from Alexion; and speaker honoraria from Alexion.

Gaelen P. Adam, MLIS, MPH, PhD, has worked as librarian, editor, and research associate at the Brown University Center for Evidence Synthesis in Health (CESH; Providence, Rhode Island, USA) since 2013. In these roles, she has been involved in all steps of the projects undertaken by CESH and has developed a deep understanding of the methods and tools used in evidence synthesis research. As a research associate and the program manager for the Brown University Evidence-based Practice Center (EPC), she has contributed to the production of over 20 evidence-synthesis products (systematic reviews, technology assessments, and other similar products) on a wide variety of clinical and public health topics. She has been a member of the ERT for 5 KDIGO guideline updates; this is her first time serving as a member of the ERT for a *de novo* KDIGO guideline.

GPA declared no competing interests.

Ian J. Saldanha, MBBS, MPH, PhD, is an Associate Professor of Epidemiology and of Health Policy and Management at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, USA. He is an expert in systematic review and clinical practice guideline methodology.

IJS declared no competing interests.

Acknowledgments

A special debt of gratitude is owed to the KDIGO Co-Chairs, Morgan Grams and Michel Jadoul, and immediate past Co-Chair Wolfgang Winkelmayer, for their invaluable oversight throughout the development of this guideline. In particular, we thank Ethan Balk, Craig Gordon, and the ERT members for their substantial contribution to the rigorous assessment of the available evidence. We acknowledge Reem A. Mustafa for her guidance on strengthening the linkage between the recommendations and evidence base, providing invaluable methodological guidance, striving to improve on the format to better meet the KDIGO aspiration for a "living guideline" that is consistently kept up-to-date, and above all, ensuring that the guideline is useful and informative to practicing healthcare providers. We also acknowledge Debbie Maizels for her vital contributions to the artwork presented in this guideline.

We are especially grateful to the Work Group members for their expertise throughout the entire process of literature review, data extraction, meeting participation, and the critical writing and editing of the statements and rationale, which made the publication of this guideline possible. The generous gift of their time and dedication is greatly appreciated. Finally, and on behalf of the Work Group, we gratefully acknowledge the careful assessment of the draft guideline by public external reviewers. The Work Group considered all of the valuable comments made, and as appropriate, suggested changes were incorporated into the final publication. The following individuals provided feedback during the public review of the draft guideline:

Sajid Abbasi, Baris Afsar, Adan Aftab, Jehad Al Laham, Farah Alabed, Maria del Carmen Alvarado, Mahmoud Amer, American Kidney Fund, S Angus, Mabel Aoun, Eugenia Arismendi, Mariano Arriola, Sebastian Baatz, Samir Babayev, Kyongtae Bae, Arvind Bagga, Meera Bajwa, Shane Balzan, Ebunoluwa Bamgboye, Robert Barker, Sharon M. Bartosh, Ezzat Bedawi, Dibyendu Bhattacharyya, Sangeeta Bhorade, Jessica Bins, David Borland, Deimante Brazdziunaite, William Brazell, Elena Brioni, Claire Brooks, Robert Brown, Dayu Bunga, Rafael Burgos Calderon, Alison Burns, Yasar Caliskan, Emily Campbell, Debra Carter, Fadia Chamma, Michel T. Chan, Alexander Chang, Fouad Chebib, Bèi Yíng Chén, P. Collins, Christian Combe, Malcolm Correia, Vanessa Cullen, Frank Czerwiec, Neera Dahl, Mustapha Dahlab, Cecilia Dall'Anese Siegenthaler, Declan de Freitas, Sreedhar Devathi, Paula Di Rienzo, Megi Dinova, Manh Ha Do, Amy Donahue, Kai-Uwe Eckardt, Jason Eckel, Carlos Egues, Amr Elbahnassawi, Margaret Ellis, Mar Espino-Hernández, André Esteves, Mota Eugen, Jeff Felice, Katharine Fiduccia, Kristina Filic, Eileen Flahive, Nora Franceschini, Margaret Freese, Monica Furlano, Hany Gad, Daniel Gale, Robert Gardos, Ranine Ghamrawi, Matt Gittus, Mateja Globokar, Roberto Gonçalves, Katriona Goode, Susan Goutcherr, Takayuki Hagiwara, Jan Halbritter, Kenneth Hallows, Christian Hanna, Nicole Harper, Nuri Baris Hasbal, Abdul Haseeb, Aws Hassan, Mohamed Hassan, Ludwig Haydock, Linda Herman, Jacqueline Hernandez, Marc Angelo Hizon, Beccy Hoddinott-Isaac, Christopher Hogan, Marie Hogan, Katarzyna Hongler, Pam Hooley, Junichi Hoshino, Min-Lun Hsieh, Kathleen Illidge, Eiji Ishikawa, Erika Bianca Isidro, Santhanam Iyer, Abraham Jaime, Manish Jain, Wasif Jamil, Margaret Johnson, Dominique Joly, Francois Jouret, Jessica Kachmar, Patrick Kamath, Nada Kanaan, Fiona Karet, Sinem Karipcin, Rümeyza Kazancıoğlu, Richard Kellner, Yavuz Erkam Kesgin, Mahmoud Kharrat, Bertrand Knebelmann, Benjamin Koch, Lyndsey Kone, Styliani Kontogianni, Uwe K.H. Korst, Anna Köttgen, Chatchai Kreepala, Sampath Kumar, Wijan Lal, Kelly Lambert, Christine Lefler, Gary Leggatt, Edgar Lerma, Elisa Llurba, Trung Lữ công, Chiara Maggioni, Peter Magill, Viyaasan Mahalingasivam, Victoria Maldonado, Tamara Malek, Partha Pratim Mandal, Andal Manfred, Katherine Maringer, Lisa McAllen, Annie McGrath, Laurent Mesnard, Anisa Mohamed, Rocely Moncayo, Pat Monz, Luis Fernando Morán Fernández, Michal Mrug, Venkata Kishore Mukku, Roman-Ulrich Müller, Mehdi Mushtaq, Abdullah Muzalef, Alessandra Naghettini, Takefumi Narikiyo, Rodica Negru, Shialor Nhiachao, Nadeesha Nishanthi, Theodoros Ntrinias, Suzanne O'Farrell, Dennis (Danny) O'Sullivan, Jana Oelkers, Ugochi Onu, Alberto Ortiz Arduan, Shohdan Osman, Noo Page, Andreea Pandelescu, Meyeon Park, Zoran Paunic, Saime Paydas, Adriana Peñalba, Nuria S. Pérez Romano, Dorien Peters, Filippo Pinto e Vairo, Evgenia Preka, Serge Querin, Frederic Rahbari-Oskoui, Swati Rao, Harun Rashid, Garett Rhule, Mary-Beth Roberts, Terry Roberts, Nicolas Roberto Robles, Joanne Rogers, Ynte Ruigrok, Maiza Saavedra, Rawan Sabbah, Rania Sadek, Krishna Kumar Sah, Ricardo San Miguel, Sagar Sarda, Sanjiv Saxena, John Sayer, Michel Schenkel, Francesco Scolari, Ammar Serawan, Beata Seymour, Mahmoud Shamma, Amita Sharma, Robert Shepard, Shekhar Shiradhonkar, Harmeet Singh, Steven Smith, Karlheinz Steinecker, Rylan Howell Superiano, Barn Sweetman, Orsolya Szathmari, James Tataw, Dianny Tavarez, Susan Taylor, Anurag Thakur, Jacob Torres, María Verónica Torres Jaramillo, Peter Trnka, Paraskevi Tseke, George Tsirpanlis, Yusuke Tsukamoto, Ercan Turkmen, Gillian Turner, Steven Van Laecke, Pamela Vasquez, Vertex Pharmaceuticals, Svetlana Villano, Mark Vishnepolsky, Eric Wallace, Alfredo Wassermann, Thomas Weimbs, Gisele Wicke, Michael Wiederkehr, Thomas Wilkinson, Kim Williams, Desalegn Wogasso, Alexander Woywodt, Mai-Szu Wu, Dawn Yates, Mina Yossef, Nelson Zamora, Stefano Zanardi, Li Zhou, Jennifer Zinetti, and Shay Zohar.

References

1. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet*. 2007;369:1287–1301.
2. Bergmann C, Guay-Woodford LM, Harris PC, et al. Polycystic kidney disease. *Nat Rev Dis Primers*. 2018;4:50.
3. Cornec-Le Gall E, Alam A, Perrone RD. Autosomal dominant polycystic kidney disease. *Lancet*. 2019;393:919–935.
4. Iliuta IA, Kalatharan V, Wang K, et al. Polycystic kidney disease without an apparent family history. *J Am Soc Nephrol*. 2017;28:2768–2776.
5. Heyer CM, Sundsbak JL, Abebe KZ, et al. Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27:2872–2884.
6. Cornec-Le Gall E, Torres VE, Harris PC. Genetic complexity of autosomal dominant polycystic kidney and liver diseases. *J Am Soc Nephrol*. 2018;29:13–23.
7. Porath B, Gainullin VG, Cornec-Le Gall E, et al. Mutations in GANAB, encoding the glucosidase IIalpha subunit, cause autosomal-dominant polycystic kidney and liver disease. *Am J Hum Genet*. 2016;98:1193–1207.
8. Cornec-Le Gall E, Olson RJ, Besse W, et al. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet*. 2018;102:832–844.
9. Besse W, Chang AR, Luo JZ, et al. ALG9 mutation carriers develop kidney and liver cysts. *J Am Soc Nephrol*. 2019;30:2091–2102.
10. Senum SR, Li YSM, Benson KA, et al. Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. *Am J Hum Genet*. 2022;109:136–156.
11. Lemoine H, Raud L, Foulquier F, et al. Monoallelic pathogenic ALG5 variants cause atypical polycystic kidney disease and interstitial fibrosis. *Am J Hum Genet*. 2022;109:1484–1499.
12. Drenth JPH, te Morsche RHM, Smink R, et al. Germline mutations in PRKCSH are associated with autosomal dominant polycystic liver disease. *Nat Genet*. 2003;33:345–347.
13. Li A, Davila S, Furu L, et al. Mutations in PRKCSH cause isolated autosomal dominant polycystic liver disease. *Am J Hum Genet*. 2003;72:691–703.
14. Davila S, Furu L, Gharavi AG, et al. Mutations in SEC63 cause autosomal dominant polycystic liver disease. *Nat Genet*. 2004;36:575–577.
15. Besse W, Dong K, Choi J, et al. Isolated polycystic liver disease genes define effectors of polycystin-1 function. *J Clin Invest*. 2017;127:1772–1785.
16. Eckardt KU, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management—a KDIGO consensus report. *Kidney Int*. 2015;88:676–683.
17. Biesecker LG, Adam MP, Alkuraya FS, et al. A dyadic approach to the delineation of diagnostic entities in clinical genomics. *Am J Hum Genet*. 2021;108:8–15.
18. Lemoine H, Raud L, Foulquier F, et al. Monoallelic pathogenic ALG5 variants cause atypical polycystic kidney disease and interstitial fibrosis. *Am J Hum Genet*. 2022;109:1484–1499.
19. Huynh VT, Audrezet MP, Sayer JA, et al. Clinical spectrum, prognosis and estimated prevalence of DNAJB11-kidney disease. *Kidney Int*. 2020;98:476–487.
20. Jordan P, Arrondel C, Bessieres B, et al. Bi-allelic pathogenic variations in DNAJB11 cause Ivemark II syndrome, a renal-hepatic-pancreatic dysplasia. *Kidney Int*. 2021;99:405–409.
21. Senum SR, Li YSM, Benson KA, et al. Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. *Am J Hum Genet*. 2022;109:136–156.
22. Claus LR, Chen C, Stallworth J, et al. Certain heterozygous variants in the kinase domain of the serine/threonine kinase NEK8 can cause an autosomal dominant form of polycystic kidney disease. *Kidney Int*. 2023;104:995–1007.
23. Boulogne F, Claus LR, Wiersma H, et al. KidneyNetwork: using kidney-derived gene expression data to predict and prioritize novel genes involved in kidney disease. *Eur J Hum Genet*. 2023;31:1300–1308.
24. Apple B, Sartori G, Moore B, et al. Individuals heterozygous for ALG8 protein-truncating variants are at increased risk of a mild cystic kidney disease. *Kidney Int*. 2023;103:607–615.
25. Chang AR, Moore BS, Luo JZ, et al. Exome sequencing of a clinical population for autosomal dominant polycystic kidney disease. *JAMA*. 2022;328:2412–2421.
26. Gunay-Aygun M, Turkbey BI, Bryant J, et al. Hepatorenal findings in obligate heterozygotes for autosomal recessive polycystic kidney disease. *Mol Genet Metab*. 2011;104:677–681.
27. Cnossen WR, te Morsche RHM, Hoischen A, et al. Whole-exome sequencing reveals LRP5 mutations and canonical Wnt signaling associated with hepatic cystogenesis. *Proc Natl Acad Sci U S A*. 2014;111:5343–5348.
28. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367:2407–2418.
29. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med*. 2017;377:1930–1942.
30. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol*. 2009;20:205–212.
31. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2015;26:746–753.
32. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol*. 2015;26:160–172.
33. Schonauer R, Sierks D, Boerrigter M, et al. Sex, genotype, and liver volume progression as risk of hospitalization determinants in autosomal dominant polycystic liver disease. *Gastroenterology*. 2024;166:902–914.
34. Cnossen WR, te Morsche RHM, Hoischen A, et al. Whole-exome sequencing reveals LRP5 mutations and canonical Wnt signaling associated with hepatic cystogenesis. *Proc Natl Acad Sci USA*. 2014;111:5343–5348.
35. Cornec-Le Gall E, Audrezet MP, Chen JM, et al. Type of PKD1 mutation influences renal outcome in ADPKD. *J Am Soc Nephrol*. 2013;24:1006–1013.
36. Cornec-Le Gall E, Audrezet MP, Rousseau A, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27:942–951.
37. Hopp K, Ward CJ, Hommerding CJ, et al. Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. *J Clin Invest*. 2012;122:4257–4273.
38. Rossetti S, Kubly VJ, Consugar MB, et al. Incompletely penetrant PKD1 alleles suggest a role for gene dosage in cyst initiation in polycystic kidney disease. *Kidney Int*. 2009;75:848–855.
39. Lanktree MB, Guiard E, Akbari P, et al. Patients with protein-truncating PKD1 mutations and mild ADPKD. *Clin J Am Soc Nephrol*. 2021;16:374–383.
40. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med*. 2019;380:142–151.
41. Yu CC, Lee AF, Kohl S, et al. PKD2 founder mutation is the most common mutation of polycystic kidney disease in Taiwan. *NPJ Genom Med*. 2022;7:40.
42. Dalgaard OZ. Bilateral polycystic disease of the kidneys: a follow-up of two hundred and eighty-four patients and their families. *Acta Med Scand*. 1957;328:1–255.
43. Aung TT, Bhandari SK, Chen Q, et al. Autosomal dominant polycystic kidney disease prevalence among a racially diverse United States population, 2002 through 2018. *Kidney360*. 2021;2:2010–2015.
44. Lanktree MB, Haghighi A, Guiard E, et al. Prevalence estimates of polycystic kidney and liver disease by population sequencing. *J Am Soc Nephrol*. 2018;29:2593–2600.
45. Neumann HP, Jilg C, Bacher J, et al. Epidemiology of autosomal-dominant polycystic kidney disease: an in-depth clinical study for south-western Germany. *Nephrol Dial Transplant*. 2013;28:1472–1487.
46. Suwabe T, Shukoor S, Chamberlain AM, et al. Epidemiology of autosomal dominant polycystic kidney disease in Olmsted County. *Clin J Am Soc Nephrol*. 2020;15:69–79.

47. Willey C, Gauthier-Loiselle M, Cloutier M, et al. Regional variations in prevalence and severity of autosomal dominant polycystic kidney disease in the United States. *Curr Med Res Opin*. 2021;37:1155–1162.
48. Willey C, Kamat S, Stellhorn R, et al. Analysis of nationwide data to determine the incidence and diagnosed prevalence of autosomal dominant polycystic kidney disease in the USA: 2013-2015. *Kidney Dis (Basel)*. 2019;5:107–117.
49. Willey CJ, Blais JD, Hall AK, et al. Prevalence of autosomal dominant polycystic kidney disease in the European Union. *Nephrol Dial Transplant*. 2017;32:1356–1363.
50. Yersin C, Bovet P, Wauters JP, et al. Frequency and impact of autosomal dominant polycystic kidney disease in the Seychelles (Indian Ocean). *Nephrol Dial Transplant*. 1997;12:2069–2074.
51. United States Renal Data System (USRDS). *2020 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2020.
52. Astley ME, Boenink R, ElHafeez SA, et al. The ERA Registry Annual Report 2020: a summary. *Clin Kidney J*. 2023;16:1330–1354.
53. Dudley J, Winyard P, Marlais M, et al. Clinical practice guideline monitoring children and young people with, or at risk of developing autosomal dominant polycystic kidney disease (ADPKD). *BMC Nephrol*. 2019;20:148.
54. Kramers BJ, Storm M, Gansevoort RT. [Autosomal dominant polycystic kidney disease: should patients' young adult relatives be screened or not?]. *Ned Tijdschr Geneeskd*. 2017;161:D1942 [in Dutch].
55. Elliott MD, James LC, Simms EL, et al. Mainstreaming genetic testing for adult patients with autosomal dominant polycystic kidney disease. *Can J Kidney Health Dis*. 2021;8:20543581211055001.
56. Odland D. A patient perspective on genetic testing for ADPKD: the lack of complete genetic information, especially early in the course of the disease, is harming adult autosomal dominant polycystic kidney disease (ADPKD) patients. *Clin J Am Soc Nephrol*. 2021;16:671–673.
57. George A, Riddell D, Seal S, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. *Sci Rep*. 2016;6:29506.
58. Bennett CL, Burke SE, Burton H, et al. A toolkit for incorporating genetics into mainstream medical services: learning from service development pilots in England. *BMC Health Serv Res*. 2010;10:125.
59. Mallett A, Corney C, McCarthy H, et al. Genomics in the renal clinic—translating nephrogenetics for clinical practice. *Hum Genomics*. 2015;9:13.
60. Mallett A, Fowles LF, McGaughran J, et al. A multidisciplinary renal genetics clinic improves patient diagnosis. *Med J Aust*. 2016;204:58–59.
61. Dahl NK, Bloom MS, Chebib FT, et al. The clinical utility of genetic testing in the diagnosis and management of adults with chronic kidney disease. *J Am Soc Nephrol*. 2023;34:2039–2050.
62. Rule AD, Sasiwimonphan K, Lieske JC, et al. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. *Am J Kidney Dis*. 2012;59:611–618.
63. Ravine D, Gibson RN, Walker RG, et al. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. *Lancet*. 1994;343:824–827.
64. Ponte B, Pruijm M, Ackermann D, et al. Copeptin is associated with kidney length, renal function, and prevalence of simple cysts in a population-based study. *J Am Soc Nephrol*. 2015;26:1415–1425.
65. Thomas CP, Daloul R, Lentine KL, et al. Genetic evaluation of living kidney donor candidates: a review and recommendations for best practices. *Am J Transplant*. 2023;23:597–607.
66. Lu W, Peissel B, Babakhanlou H, et al. Perinatal lethality with kidney and pancreas defects in mice with a targeted *Pkd1* mutation. *Nat Genet*. 1997;17:179–181.
67. Vujic M, Heyer CM, Ars E, et al. Incompletely penetrant PKD1 alleles mimic the renal manifestations of ARPKD. *J Am Soc Nephrol*. 2010;21:1097–1102.
68. Bergmann C, von Bothmer J, Ortiz Bruchle N, et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. *J Am Soc Nephrol*. 2011;22:2047–2056.
69. Audrezet MP, Corbiere C, Lebbah S, et al. Comprehensive PKD1 and PKD2 mutation analysis in prenatal autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2016;27:722–729.
70. Durkie M, Chong J, Valluru MK, et al. Biallelic inheritance of hypomorphic PKD1 variants is highly prevalent in very early onset polycystic kidney disease. *Genet Med*. 2021;23:689–697.
71. Al-Hamed MH, Alsahan N, Rice SJ, et al. Bialleleic PKD1 mutations underlie early-onset autosomal dominant polycystic kidney disease in Saudi Arabian families. *Pediatr Nephrol*. 2019;34:1615–1623.
72. Pei Y, Paterson AD, Wang KR, et al. Bilineal disease and trans-heterozygotes in autosomal dominant polycystic kidney disease. *Am J Hum Genet*. 2001;68:355–363.
73. Hwang YH, Conklin J, Chan W, et al. Refining genotype-phenotype correlation in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2015;27:1861–1868.
74. Losekoot M, Meijer E, Hagen EC, et al. Polycystic kidney disease caused by bilineal inheritance of truncating PKD1 as well as PKD2 mutations. *Kidney Int Rep*. 2020;5:1828–1832.
75. Rossetti S, Strmecki L, Gamble V, et al. Mutation analysis of the entire PKD1 gene: genetic and diagnostic implications. *Am J Hum Genet*. 2001;68:46–63.
76. Hopp K, Cornec-Le Gall E, Senum SR, et al. Detection and characterization of mosaicism in autosomal dominant polycystic kidney disease. *Kidney Int*. 2020;97:370–382.
77. Connor A, Lunt PW, Dolling C, et al. Mosaicism in autosomal dominant polycystic kidney disease revealed by genetic testing to enable living related renal transplantation. *Am J Transplant*. 2008;8:232–237.
78. Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. *N Engl J Med*. 2011;364:1533–1543.
79. McConnachie DJ, Stow JL, Mallett AJ. Ciliopathies and the kidney: a review. *Am J Kidney Dis*. 2021;77:410–419.
80. Pezzella N, Bove G, Tammaro R, et al. OFD1: one gene, several disorders. *Am J Med Genet C Semin Med Genet*. 2022;190:57–71.
81. Bockenhauer D, Jaureguiberry G. HNF1B-associated clinical phenotypes: the kidney and beyond. *Pediatr Nephrol*. 2016;31:707–714.
82. Semenova N, Kamenets E, Annenkova E, et al. Clinical characterization of Alagille syndrome in patients with cholestatic liver disease. *Int J Mol Sci*. 2023;24:11758.
83. Burgmaier K, Brinker L, Erger F, et al. Refining genotype-phenotype correlations in 304 patients with autosomal recessive polycystic kidney disease and PKHD1 gene variants. *Kidney Int*. 2021;100:650–659.
84. Adeva M, El-Youssef M, Rossetti S, et al. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). *Medicine (Baltimore)*. 2006;85:1–21.
85. Nair N, Chakraborty R, Mahajan Z, et al. Renal manifestations of tuberous sclerosis complex. *J Kidney Cancer VHL*. 2020;7:5–19.
86. van Leeuwaarde RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews® [Internet]*. University of Washington, Seattle; 1993–2023. Accessed July 10, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1463/
87. Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dube syndrome. *Nat Rev Urol*. 2015;12:558–569.
88. Schonauer R, Baatz S, Nemitz-Kliemchen M, et al. Matching clinical and genetic diagnoses in autosomal dominant polycystic kidney disease reveals novel phenocopies and potential candidate genes. *Genet Med*. 2020;22:1374–1383.
89. Lehtonen HJ, Kiuru M, Ylisaukko-Oja SK, et al. Increased risk of cancer in patients with fumarate hydratase germline mutation. *J Med Genet*. 2006;43:523–526.
90. Brook-Carter PT, Peral B, Ward CJ, et al. Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease—a contiguous gene syndrome. *Nat Genet*. 1994;8:328–332.
91. Sampson JR, Maheshwar MM, Aspinwall R, et al. Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene. *Am J Hum Genet*. 1997;61:843–851.
92. Kashtan CE, Ding J, Garosi G, et al. Alport syndrome: a unified classification of genetic disorders of collagen IV alpha345: a position paper of the Alport Syndrome Classification Working Group. *Kidney Int*. 2018;93:1045–1051.
93. Gulati A, Sevillano AM, Praga M, et al. Collagen IV gene mutations in adults with bilateral renal cysts and CKD. *Kidney Int Rep*. 2020;5:103–108.
94. Bada-Bosch T, Sevillano AM, Teresa Sanchez-Calvin M, et al. Cystic phenotype and chronic kidney disease in autosomal dominant Alport syndrome. *Nephrol Dial Transplant*. 2024;39:1288–1298.
95. Devuyst O, Olinger E, Weber S, et al. Autosomal dominant tubulointerstitial kidney disease. *Nat Rev Dis Primers*. 2019;5:60.
96. Olinger E, Hofmann P, Kidd K, et al. Clinical and genetic spectra of autosomal dominant tubulointerstitial kidney disease due to mutations in UMOD and MUC1. *Kidney Int*. 2020;98:717–731.

97. Rahbari-Oskoui F, O'Neill WC. Diagnosis and management of acquired cystic kidney disease and renal tumors in ESRD patients. *Semin Dial*. 2017;30:373–379.
98. Pawar AS, Kattah AG. Lithium-induced nephropathy. *N Engl J Med*. 2018;378:1042.
99. Cornec-Le Gall E, Chebib FT, Madsen CD, et al. The value of genetic testing in polycystic kidney diseases illustrated by a family with PKD2 and COL4A1 mutations. *Am J Kidney Dis*. 2018;72:302–308.
100. Gulati A, Bae KT, Somlo S, et al. Genomic analysis to avoid misdiagnosis of adults with bilateral renal cysts. *Ann Intern Med*. 2018;169:130–131.
101. Hanna C, Potretzke TA, Cogal AG, et al. High prevalence of kidney cysts in patients with CYP24A1 deficiency. *Kidney Int Rep*. 2021;6:1895–1903.
102. Hanna C, Potretzke TA, Chedid M, et al. Kidney cysts in hypophosphatemic rickets with hypercalciuria: a case series. *Kidney Med*. 2022;4:100419.
103. Patel DM, Page N, Dahl NK. Kidney cysts in patients with HOGA1 variants. *Clin Nephrol*. 2023;99:260–264.
104. Phakdeekitcharoen B, Watnick T, Germino GG. Mutation analysis of the entire replicated portion of *PKD1* using genomic DNA samples. *J Am Soc Nephrol*. 2001;12:955–963.
105. Trujillano D, Bullich G, Ossowski S, et al. Diagnosis of autosomal dominant polycystic kidney disease using efficient PKD1 and PKD2 targeted next-generation sequencing. *Mol Genet Genomic Med*. 2014;2:412–421.
106. Eisenberger T, Decker C, Hiersche M, et al. An efficient and comprehensive strategy for genetic diagnostics of polycystic kidney disease. *PLoS One*. 2015;10:e0116680.
107. Ali H, Al-Mulla F, Hussain N, et al. PKD1 duplicated regions limit clinical utility of whole exome sequencing for genetic diagnosis of autosomal dominant polycystic kidney disease. *Sci Rep*. 2019;9:4141.
108. Mallawaarachchi AC, Hort Y, Cowley MJ, et al. Whole-genome sequencing overcomes pseudogene homology to diagnose autosomal dominant polycystic kidney disease. *Eur J Hum Genet*. 2016;24:1584–1590.
109. Mallawaarachchi AC, Lundie B, Hort Y, et al. Genomic diagnostics in polycystic kidney disease: an assessment of real-world use of whole-genome sequencing. *Eur J Hum Genet*. 2021;29:760–770.
110. KDIGO conference participants. Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2022;101:1126–1141.
111. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424.
112. Stenson PD, Mort M, Ball EV, et al. The Human Gene Mutation Database: building a comprehensive mutation repository for clinical and molecular genetics, diagnostic testing and personalized genomic medicine. *Hum Genet*. 2014;133:1–9.
113. Frangioni JV, Cowley MJ, Harris PC, et al. The autosomal dominant polycystic kidney disease mutation database. *Nat Genet*. 2018;50:901–907.
114. Gabow PA, Johnson AM, Kaehny WD, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. *Kidney Int*. 1992;41:1311–1319.
115. Lavu S, Vaughan LE, Senum SR, et al. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. *JCI Insight*. 2020;5:e138724.
116. Zerres K, Rudnik-Schoneborn S, Deget F. Childhood onset autosomal dominant polycystic kidney disease in sibs: clinical picture and recurrence risk. German Working Group on Paediatric Nephrology (Arbeitsgemeinschaft fur Padiatrische Nephrologie. *J Med Genet*. 1993;30:583–588.
117. Lanktree MB, Guiard E, Li W, et al. Intrafamilial variability of ADPKD. *Kidney Int Rep*. 2019;4:995–1003.
118. Persu A, Duyme M, Pirson Y, et al. Comparison between siblings and twins supports a role for modifier genes in ADPKD. *Kidney Int*. 2004;66:2132–2136.
119. Gainullin VG, Hopp K, Ward CJ, et al. Polycystin-1 maturation requires polycystin-2 in a dose-dependent manner. *J Clin Invest*. 2015;125:607–620.
120. Olson RJ, Hopp K, Wells H, et al. Synergistic genetic interactions between Pkhd1 and Pkd1 result in an ARPKD-like phenotype in murine models. *J Am Soc Nephrol*. 2019;30:2113–2127.
121. Khan A, Shang N, Nestor JG, et al. Polygenic risk alters the penetrance of monogenic kidney disease. *Nat Commun*. 2023;14:8318.
122. Qian F, Watnick TJ, Onuchic LF, et al. The molecular basis of focal cyst formation in human autosomal dominant polycystic kidney disease type I. *Cell*. 1996;87:979–987.
123. Brasier JL, Henske EP. Loss of the polycystic kidney disease (PKD1) region of chromosome 16p13 in renal cyst cells supports a loss-of-function model for cyst pathogenesis. *J Clin Invest*. 1997;99:194–199.
124. Tan AY, Zhang T, Michaeel A, et al. Somatic mutations in renal cyst epithelium in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2018;29:2139–2156.
125. Zhang Z, Bai H, Blumenfeld J, et al. Detection of PKD1 and PKD2 somatic variants in autosomal dominant polycystic kidney cyst epithelial cells by whole-genome sequencing. *J Am Soc Nephrol*. 2021;32:3114–3129.
126. Sousa MV, Amaral AG, Freitas JA, et al. Smoking accelerates renal cystic disease and worsens cardiac phenotype in Pkd1-deficient mice. *Sci Rep*. 2021;11:14443.
127. McKenzie KA, El Ters M, Torres VE, et al. Relationship between caffeine intake and autosomal dominant polycystic kidney disease progression: a retrospective analysis using the CRISP cohort. *BMC Nephrol*. 2018;19:378.
128. Girardat-Rotar L, Puhan MA, Braun J, et al. Long-term effect of coffee consumption on autosomal dominant polycystic kidneys disease progression: results from the Suisse ADPKD, a Prospective Longitudinal Cohort Study. *J Nephrol*. 2018;31:87–94.
129. Meca R, Balbo BE, Ormanji MS, et al. Caffeine accelerates cystic kidney disease in a Pkd1-deficient mouse model. *Cell Physiol Biochem*. 2019;52:1061–1074.
130. Happe H, Leonhard WN, van der Wal A, et al. Toxic tubular injury in kidneys from Pkd1-deletion mice accelerates cystogenesis accompanied by dysregulated planar cell polarity and canonical Wnt signaling pathways. *Hum Mol Genet*. 2009;18:2532–2542.
131. Takakura A, Contrino L, Zhou X, et al. Renal injury is a third hit promoting rapid development of adult polycystic kidney disease. *Hum Mol Genet*. 2009;18:2523–2531.
132. Shukoor SS, Vaughan LE, Edwards ME, et al. Characteristics of patients with end-stage kidney disease in ADPKD. *Kidney Int Rep*. 2021;6:755–767.
133. Hateboer N, van Dijk MA, Bogdanova N, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. *Lancet*. 1999;353:103–107.
134. Cornec-Le Gall E, Audrezet MP, Renaudineau E, et al. PKD2-related autosomal dominant polycystic kidney disease: prevalence, clinical presentation, mutation spectrum, and prognosis. *Am J Kidney Dis*. 2017;70:476–485.
135. Barua M, Cil O, Paterson AD, et al. Family history of renal disease severity predicts the mutated gene in ADPKD. *J Am Soc Nephrol*. 2009;20:1833–1838.
136. Warner G, Hein KZ, Nin V, et al. Food restriction ameliorates the development of polycystic kidney disease. *J Am Soc Nephrol*. 2016;27:1437–1447.
137. Kipp KR, Rezaei M, Lin L, et al. A mild reduction of food intake slows disease progression in an orthologous mouse model of polycystic kidney disease. *Am J Physiol Renal Physiol*. 2016;310:F726–F731.
138. Torres JA, Kruger SL, Broderick C, et al. Ketosis ameliorates renal cyst growth in polycystic kidney disease. *Cell Metab*. 2019;30:1007–1023.e5.
139. Nagao S, Nishii K, Katsuyama M, et al. Increased water intake decreases progression of polycystic kidney disease in the PCK rat. *J Am Soc Nephrol*. 2006;17:2220–2227.
140. Nowak KL, You Z, Gitomer B, et al. Overweight and obesity are predictors of progression in early autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2018;29:571–578.
141. Torres VE, Abebe KZ, Schrier RW, et al. Dietary salt restriction is beneficial to the management of autosomal dominant polycystic kidney disease. *Kidney Int*. 2017;91:493–500.
142. Kramers BJ, Koorevaar IW, Drenth JPH, et al. Salt, but not protein intake, is associated with accelerated disease progression in autosomal dominant polycystic kidney disease. *Kidney Int*. 2020;98:989–998.
143. Grantham JJ, Torres VE, Chapman AB, et al. Volume progression in polycystic kidney disease. *N Engl J Med*. 2006;354:2122–2130.
144. King BF, Torres VE, Brummer ME, et al. Magnetic resonance measurements of renal blood flow as a marker of disease severity in autosomal-dominant polycystic kidney disease. *Kidney Int*. 2003;64:2214–2221.
145. Torres VE, King BF, Chapman AB, et al. Magnetic resonance measurements of renal blood flow and disease progression in

autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2007;2:112–120.
146. Brenner DJ, Doll R, Goodhead DT, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proc Natl Acad Sci U S A*. 2003;100:13761–13766.
147. Bae KT, Commean PK, Lee J. Volumetric measurement of renal cysts and parenchyma using MRI: phantoms and patients with polycystic kidney disease. *J Comput Assist Tomogr*. 2000;24:614–619.
148. King BF, Reed JE, Bergstralh EJ, et al. Quantification and longitudinal trends of kidney, renal cyst, and renal parenchyma volumes in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2000;11:1505–1511.
149. Kistler AD, Poster D, Krauer F, et al. Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months. *Kidney Int*. 2009;75:235–241.
150. Kline TL, Korfiatis P, Edwards ME, et al. Automatic total kidney volume measurement on follow-up magnetic resonance images to facilitate monitoring of autosomal dominant polycystic kidney disease progression. *Nephrol Dial Transplant*. 2016;31:241–248.
151. Kline TL, Korfiatis P, Edwards ME, et al. Performance of an artificial multi-observer deep neural network for fully automated segmentation of polycystic kidneys. *J Digit Imaging*. 2017;30:442–448.
152. Chapman AB, Bost JE, Torres VE, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2012;7:479–486.
153. Yu ASL, Shen C, Landsittel DP, et al. Baseline total kidney volume and the rate of kidney growth are associated with chronic kidney disease progression in autosomal dominant polycystic kidney disease. *Kidney Int*. 2018;93:691–699.
154. Akbari A, Tangri N, Brown PA, et al. Prediction of progression in polycystic kidney disease using the kidney failure risk equation and ultrasound parameters. *Can J Kidney Health Dis*. 2020;7:2054358120911274.
155. Bae KT, Shi T, Tao C, et al. Expanded imaging classification of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2020;31:1640–1651.
156. Bhutani H, Smith V, Rahbari-Oskoui F, et al. A comparison of ultrasound and magnetic resonance imaging shows that kidney length predicts chronic kidney disease in autosomal dominant polycystic kidney disease. *Kidney Int*. 2015;88:146–151.
157. Boertien WE, Meijer E, Li J, et al. Relationship of copeptin, a surrogate marker for arginine vasopressin, with change in total kidney volume and GFR decline in autosomal dominant polycystic kidney disease: results from the CRISP cohort. *Am J Kidney Dis*. 2013;61:420–429.
158. Boertien WE, Meijer E, Zittema D, et al. Copeptin, a surrogate marker for vasopressin, is associated with kidney function decline in subjects with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2012;27:4131–4137.
159. Borrego Utiel FJ, Esteban de la Rosa RJ, Merino Garcia E, et al. Predicting future renal function decline in patients with autosomal dominant polycystic kidney disease using Mayo Clinic classification. *Am J Nephrol*. 2021;52:630–641.
160. Brosnahan GM, You Z, Wang W, et al. Serum uric acid and progression of autosomal dominant polycystic kidney disease: results from the HALT PKD trials. *Curr Hypertens Rev*. 2021;17:228–237.
161. Casteleijn NF, Zittema D, Bakker SJ, et al. Urine and plasma osmolality in patients with autosomal dominant polycystic kidney disease: reliable indicators of vasopressin activity and disease prognosis? *Am J Nephrol*. 2015;41:248–256.
162. Chen D, Ma Y, Wang X, et al. Clinical characteristics and disease predictors of a large Chinese cohort of patients with autosomal dominant polycystic kidney disease. *PLoS One*. 2014;9:e92232.
163. Dehesa-López E, Pérez-Gutiérrez RA, Valdez-Ortiz R, et al. [Clinical and laboratorial predictors related to progression to chronic kidney disease in patients with autosomal dominant polycystic kidney disease]. *Rev Invest Clin*. 2009;61:364–370 [in Spanish].
164. Dekker SEI, Verhoeven A, Soonawala D, et al. Urinary metabolites associate with the rate of kidney function decline in patients with autosomal dominant polycystic kidney disease. *PLoS One*. 2020;15:e0233213.
165. Han M, Park HC, Kim H, et al. Hyperuricemia and deterioration of renal function in autosomal dominant polycystic kidney disease. *BMC Nephrol*. 2014;15:63.
166. Harskamp LR, Perez-Gomez MV, Heida JE, et al. The association of urinary epidermal growth factors with ADPKD disease severity and progression. *Nephrol Dial Transplant*. 2023;38:2266–2275.
167. Heida JE, Gansevoort RT, Messchendorp AL, et al. Use of the urine-to-plasma urea ratio to predict ADPKD progression. *Clin J Am Soc Nephrol*. 2021;16:204–212.
168. Helal I, McFann K, Reed B, et al. Serum uric acid, kidney volume and progression in autosomal-dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2013;28:380–385.
169. Hwang JH, Park HC, Jeong JC, et al. Chronic asymptomatic pyuria precedes overt urinary tract infection and deterioration of renal function in autosomal dominant polycystic kidney disease. *BMC Nephrol*. 2013;14:1.
170. Johnson AM, Gabow PA. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. *J Am Soc Nephrol*. 1997;8:1560–1567.
171. Kocyigit I, Eroglu E, Kaynar AS, et al. The association of endothelin-1 levels with renal survival in polycystic kidney disease patients. *J Nephrol*. 2019;32:83–91.
172. Kocyigit I, Ozturk F, Eroglu E, et al. Dysmetabolic markers predict outcomes in autosomal dominant polycystic kidney disease. *Clin Exp Nephrol*. 2019;23:1130–1140.
173. Kocyigit I, Sener EF, Taheri S, et al. Toll-like receptors in the progression of autosomal dominant polycystic kidney disease. *Ther Apher Dial*. 2016;20:615–622.
174. Kocyigit I, Taheri S, Sener EF, et al. Serum micro-rna profiles in patients with autosomal dominant polycystic kidney disease according to hypertension and renal function. *BMC Nephrol*. 2017;18:179.
175. Lacquaniti A, Chirico V, Lupica R, et al. Apelin and copeptin: two opposite biomarkers associated with kidney function decline and cyst growth in autosomal dominant polycystic kidney disease. *Peptides*. 2013;49:1–8.
176. Malakoutian T, Izadi S, Honarpisheh P, et al. Estimating patient survival and risk of end-stage kidney disease in patients with autosomal dominant polycystic kidney disease in Iran. *Iran J Kidney Dis*. 2023;17:141–149.
177. McEwan P, Bennett Wilton H, Ong ACM, et al. A model to predict disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD): the ADPKD Outcomes Model. *BMC Nephrol*. 2018;19:37.
178. Messchendorp AL, Spithoven EM, Casteleijn NF, et al. Association of plasma somatostatin with disease severity and progression in patients with autosomal dominant polycystic kidney disease. *BMC Nephrol*. 2018;19:368.
179. Oh YK, Ryu H, Ahn C, et al. Clinical characteristics of rapid progression in Asia-Pacific patients with ADPKD. *Kidney Int Rep*. 2023;8:1801–1810.
180. Orskov B, Christensen KB, Feldt-Rasmussen B, et al. Low birth weight is associated with earlier onset of end-stage renal disease in Danish patients with autosomal dominant polycystic kidney disease. *Kidney Int*. 2012;81:919–924.
181. Ozkok A, Akpinar TS, Tufan F, et al. Clinical characteristics and predictors of progression of chronic kidney disease in autosomal dominant polycystic kidney disease: a single center experience. *Clin Exp Nephrol*. 2013;17:345–351.
182. Panizo N, Goicoechea M, Garcia de Vinuesa S, et al. Chronic kidney disease progression in patients with autosomal dominant polycystic kidney disease. *Nefrologia*. 2012;32:197–205.
183. Park H, Paek JH, Kim Y, et al. Clinical characteristics and risk factors for kidney failure in patients with autosomal dominant polycystic kidney disease: a retrospective study. *Medicine (Baltimore)*. 2022;101:e31838.
184. Park HC, Kim J, Cho A, et al. Urinary angiotensinogen in addition to imaging classification in the prediction of renal outcome in autosomal dominant polycystic kidney disease. *J Korean Med Sci*. 2020;35:e165.
185. Perrone RD, Abebe KZ, Watnick TJ, et al. Primary results of the randomized trial of metformin administration in polycystic kidney disease (TAME PKD). *Kidney Int*. 2021;100:684–696.
186. Perrone RD, Mouksassi MS, Romero K, et al. Total kidney volume is a prognostic biomarker of renal function decline and progression to end-stage renal disease in patients with autosomal dominant polycystic kidney disease. *Kidney Int Rep*. 2017;2:442–450.
187. Riyahi S, Dev H, Blumenfeld JD, et al. Hemorrhagic cysts and other MR biomarkers for predicting renal dysfunction progression in autosomal dominant polycystic kidney disease. *J Magn Reson Imaging*. 2021;53:564–576.

188. Sato M, Kataoka H, Ushio Y, et al. High serum phosphate level as a risk factor to determine renal prognosis in autosomal dominant polycystic kidney disease: a retrospective study. *Medicines (Basel)*. 2020;7:13.
189. Sekine A, Fujimaru T, Hoshino J, et al. Genotype-clinical correlations in polycystic kidney disease with no apparent family history. *Am J Nephrol*. 2019;49:233–240.
190. Thong KM, Ong AC. The natural history of autosomal dominant polycystic kidney disease: 30-year experience from a single centre. *QJM*. 2013;106:639–646.
191. Uchiyama K, Mochizuki T, Shimada Y, et al. Factors predicting decline in renal function and kidney volume growth in autosomal dominant polycystic kidney disease: a prospective cohort study (Japanese Polycystic Kidney Disease registry: J-PKD). *Clin Exp Nephrol*. 2021;25:970–980.
192. Ushio Y, Kataoka H, Sato M, et al. Association between anemia and renal prognosis in autosomal dominant polycystic kidney disease: a retrospective study. *Clin Exp Nephrol*. 2020;24:500–508.
193. O'Neill WC, Robbin ML, Bae KT, et al. Sonographic assessment of the severity and progression of autosomal dominant polycystic kidney disease: the Consortium of Renal Imaging Studies in Polycystic Kidney Disease (CRISP). *Am J Kidney Dis*. 2005;46:1058–1064.
194. Naranjo J, Furlano M, Torres F, et al. Comparative analysis of tools to predict rapid progression in autosomal dominant polycystic kidney disease. *Clin Kidney J*. 2022;15:912–921.
195. Akbari P, Nasri F, Deng SX, et al. Total kidney volume measurements in ADPKD by 3D and ellipsoid ultrasound in comparison with magnetic resonance imaging. *Clin J Am Soc Nephrol*. 2022;17:827–834.
196. Chong J, Harris T, Ong ACM. Regional variation in tolvaptan prescribing across England: national data and retrospective evaluation from an expert centre. *Clin Kidney J*. 2023;16:61–68.
197. Chen EWC, Chong J, Valluru MK, et al. Combining genotype with height-adjusted kidney length predicts rapid progression of ADPKD. *Nephrol Dial Transplant*. 2024;39:956–966.
198. Yu ASL, Shen C, Landsittel DP, et al. Long-term trajectory of kidney function in autosomal-dominant polycystic kidney disease. *Kidney Int*. 2019;95:1253–1261.
199. Simms RJ, Doshi T, Metherall P, et al. A rapid high-performance semi-automated tool to measure total kidney volume from MRI in autosomal dominant polycystic kidney disease. *Eur Radiol*. 2019;29:4188–4197.
200. Cornec-Le Gall E, Blais JD, Irazabal MV, et al. Can we further enrich autosomal dominant polycystic kidney disease clinical trials for rapidly progressive patients? Application of the PROPKD score in the TEMPO trial. *Nephrol Dial Transplant*. 2018;33:645–652.
201. Kline TL, Korfiatis P, Edwards ME, et al. Image texture features predict renal function decline in patients with autosomal dominant polycystic kidney disease. *Kidney Int*. 2017;92:1206–1216.
202. Gregory AV, Chebib F, Poudyal B, et al. Utility of new image-derived biomarkers for autosomal dominant polycystic kidney disease prognosis using automated instance cyst segmentation. *Kidney Int*. 2023;104:334–342.
203. Klahr S, Breyer JA, Beck GJ, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Renal Disease Study Group. *J Am Soc Nephrol*. 1995;5:2037–2047.
204. Muller RU, Messchendorp AL, Birn H, et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. *Nephrol Dial Transplant*. 2022;37:825–839.
205. Schrier RW, Abebe KZ, Perrone RD, et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371:2255–2266.
206. Torres VE, Abebe KZ, Chapman AB, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371:2267–2276.
207. Parikh CR, Dahl NK, Chapman AB, et al. Evaluation of urine biomarkers of kidney injury in polycystic kidney disease. *Kidney Int*. 2012;81:784–790.
208. Kistler AD, Serra AL, Siwy J, et al. Urinary proteomic biomarkers for diagnosis and risk stratification of autosomal dominant polycystic kidney disease: a multicentric study. *PLoS One*. 2013;8:e53016.
209. Hogan MC, Bakeberg JL, Gainullin VG, et al. Identification of biomarkers for PKD1 using urinary exosomes. *J Am Soc Nephrol*. 2015;26:1661–1670.
210. Messchendorp AL, Meijer E, Visser FW, et al. Rapid progression of autosomal dominant polycystic kidney disease: urinary biomarkers as predictors. *Am J Nephrol*. 2019;50:375–385.
211. Zacchia M, Marchese E, Trani EM, et al. Proteomics and metabolomics studies exploring the pathophysiology of renal dysfunction in autosomal dominant polycystic kidney disease and other ciliopathies. *Nephrol Dial Transplant*. 2019;35:1853–1861.
212. Magayr TA, Song X, Streets AJ, et al. Global microRNA profiling in human urinary exosomes reveals novel disease biomarkers and cellular pathways for autosomal dominant polycystic kidney disease. *Kidney Int*. 2020;98:420–435.
213. Rocchetti MT, Pesce F, Matino S, et al. Urinary epidermal growth factor/monocyte chemotactic peptide 1 ratio as non-invasive predictor of Mayo clinic imaging classes in autosomal dominant polycystic kidney disease. *J Nephrol*. 2023;36:987–997.
214. Gabow PA, Chapman AB, Johnson AM, et al. Renal structure and hypertension in autosomal dominant polycystic kidney disease. *Kidney Int*. 1990;38:1177–1180.
215. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int*. 2021;99:S1–S87.
216. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2022;102:S1–S127.
217. Gul CB, Yildiz A, Sag S, et al. The effect of smoking on endothelial dysfunction in autosomal dominant polycystic kidney disease patients with preserved renal function. *Ren Fail*. 2021;43:1124–1129.
218. Cadnapaphornchai MA, McFann K, Strain JD, et al. Prospective change in renal volume and function in children with ADPKD. *Clin J Am Soc Nephrol*. 2009;4:820–829.
219. Schrier R, McFann K, Johnson A, et al. Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study. *J Am Soc Nephrol*. 2002;13:1733–1739.
220. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116.
221. Vasileva VY, Sultanova RF, Sudarikova AV, et al. Insights into the molecular mechanisms of polycystic kidney diseases. *Front Physiol*. 2021;12:693130.
222. Ecder T, Edelstein CL, Fick-Brosnahan GM, et al. Diuretics versus angiotensin-converting enzyme inhibitors in autosomal dominant polycystic kidney disease. *Am J Nephrol*. 2001;21:98–103.
223. Nakamura T, Sato E, Fujiwara N, et al. Changes in urinary albumin excretion, inflammatory and oxidative stress markers in ADPKD patients with hypertension. *Am J Med Sci*. 2012;343:46–51.
224. Nutahara K, Higashihara E, Horie S, et al. Calcium channel blocker versus angiotensin II receptor blocker in autosomal dominant polycystic kidney disease. *Nephron Clin Pract*. 2005;99:c18–23.
225. Ulusoy S, Ozkan G, Orem C, et al. A comparison of the effects of ramipril and losartan on blood pressure control and left ventricle hypertrophy in patients with autosomal dominant polycystic kidney disease. *Ren Fail*. 2010;32:913–917.
226. Zeltner R, Poliak R, Stiasny B, et al. Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2008;23:573–579.
227. van Dijk MA, Breuning MH, Duiser R, et al. No effect of enalapril on progression in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2003;18:2314–2320.
228. Gabow PA. Autosomal dominant polycystic kidney disease. *N Engl J Med*. 1993;329:332–342.
229. Hogan MC, Norby SM. Evaluation and management of pain in autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis*. 2010;17:e1–e16.
230. Miskulin DC, Abebe KZ, Chapman AB, et al. Health-related quality of life in patients with autosomal dominant polycystic kidney disease and CKD stages 1-4: a cross-sectional study. *Am J Kidney Dis*. 2014;63:214–226.
231. Casteleijn NF, van Gastel MD, Blankestijn PJ, et al. Novel treatment protocol for ameliorating refractory, chronic pain in patients with autosomal dominant polycystic kidney disease. *Kidney Int*. 2017;91:972–981.
232. Bajwa ZH, Gupta S, Warfield CA, et al. Pain management in polycystic kidney disease. *Kidney Int*. 2001;60:1631–1644.

233. El-Damanawi R, Lee M, Harris T, et al. Developing a patient-centred tool for pain measurement and evaluation in autosomal dominant polycystic kidney disease. *Clin Kidney J*. 2021;14:2338–2348.
234. van Luijk F, Gansevoort RT, Blokzijl H, et al. Multidisciplinary management of chronic refractory pain in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2023;38:618–629.
235. World Health Organization. *WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents*. World Health Organization; 2019.
236. Little P, Lewith G, Webley F, et al. Randomised controlled trial of Alexander technique lessons, exercise, and massage (ATEAM) for chronic and recurrent back pain. *BMJ*. 2008;337:a884.
237. Kidney Disease: Improving Global Outcomes CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int*. 2024;105:S117–S314.
238. Casteleijn NF, Visser FW, Drenth JP, et al. A stepwise approach for effective management of chronic pain in autosomal-dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2014;29(Suppl 4):iv142–153.
239. Genova A, Dix O, Thakur M, et al. Chronic non-cancer pain management and addiction: a review. *Cureus*. 2020;12:e6963.
240. Tellman MW, Bahler CD, Shumate AM, et al. Management of pain in autosomal dominant polycystic kidney disease and anatomy of renal innervation. *J Urol*. 2015;193:1470–1478.
241. Steinman TI, Parikh SM. In: Perrone R, Taylor EN, eds. *Autosomal dominant polycystic kidney disease (ADPKD): pain syndromes*. UpToDate; 2022.
242. Fryczkowski M, Huk J, Sitko-Saucha A, et al. [Place of laparoscopic cysts decortication (LCD) in the treatment of autosomal dominant polycystic kidney disease (AD PKD)]. *Prog Urol*. 2007;17:1324–1327.
243. Haseebuddin M, Tanagho YS, Millar M, et al. Long-term impact of laparoscopic cyst decortication on renal function, hypertension and pain control in patients with autosomal dominant polycystic kidney disease. *J Urol*. 2012;188:1239–1244.
244. Iliuta IA, Shi B, Pourafkari M, et al. Foam sclerotherapy for cyst volume reduction in autosomal dominant polycystic kidney disease: a prospective cohort study. *Kidney Med*. 2019;1:366–375.
245. de Jager RL, Casteleijn NF, de Beus E, et al. Catheter-based renal denervation as therapy for chronic severe kidney-related pain. *Nephrol Dial Transplant*. 2018;33:614–619.
246. Collini A, Benigni R, Ruggieri G, et al. Laparoscopic nephrectomy for massive kidneys in polycystic kidney disease. *JSLS*. 2021;25:e2020.00107.
247. Torres VE, Wilson DM, Hattery RR, et al. Renal stone disease in autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 1993;22:513–519.
248. Kalatharan V, Grewal G, Nash DM, et al. Stone prevalence in autosomal dominant polycystic kidney disease: a systematic review and meta-analysis. *Can J Kidney Health Dis*. 2020;7:2054358120934628.
249. Grampsas SA, Chandhoke PS, Fan J, et al. Anatomic and metabolic risk factors for nephrolithiasis in patients with autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 2000;36:53–57.
250. Nishiura JL, Neves RF, Eloi SR, et al. Evaluation of nephrolithiasis in autosomal dominant polycystic kidney disease patients. *Clin J Am Soc Nephrol*. 2009;4:838–844.
251. Singh P, Enders FT, Vaughan LE, et al. Stone composition among first-time symptomatic kidney stone formers in the community. *Mayo Clin Proc*. 2015;90:1356–1365.
252. Bhojani N, Bjazevic J, Wallace B, et al. UPDATE—Canadian Urological Association guideline: evaluation and medical management of kidney stones. *Can Urol Assoc J*. 2022;16:175–188.
253. Borghi L, Meschi T, Amato F, et al. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol*. 1996;155:839–843.
254. Cheungpasitporn W, Rossetti S, Friend K, et al. Treatment effect, adherence, and safety of high fluid intake for the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. *J Nephrol*. 2016;29:211–219.
255. Fink HA, Akornor JW, Garimella PS, et al. Diet, fluid, or supplements for secondary prevention of nephrolithiasis: a systematic review and meta-analysis of randomized trials. *Eur Urol*. 2009;56:72–80.
256. Wang X, Xu X, Wu J, et al. Systematic review and meta-analysis of the effect of alcohol intake on the risk of urolithiasis including dose-response relationship. *Urol Int*. 2015;94:194–204.
257. Rangan GK, Wong ATY, Munt A, et al. Prescribed water intake in autosomal dominant polycystic kidney disease. *NEJM Evid*. 2022;1:EVIDoa2100021.
258. Torres VE, Bankir L, Grantham JJ. A case for water in the treatment of polycystic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:1140–1150.
259. Kocvara R, Plasgura P, Petrik A, et al. A prospective study of nonmedical prophylaxis after a first kidney stone. *BJU Int*. 1999;84:393–398.
260. Kalatharan V, Jandoc R, Grewal G, et al. Efficacy and safety of surgical kidney stone interventions in autosomal dominant polycystic kidney disease: a systematic review. *Can J Kidney Health Dis*. 2020;7:2054358120940433.
261. Dalbeth N, Gosling AL, Gaffo A, et al. Gout. *Lancet*. 2021;397:1843–1855.
262. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology guideline for the management of gout. *Arthritis Care Res (Hoboken)*. 2020;72:744–760.
263. Vargas-Santos AB, Neogi T. Management of gout and hyperuricemia in CKD. *Am J Kidney Dis*. 2017;70:422–439.
264. Gabow PA, Duley I, Johnson AM. Clinical profiles of gross hematuria in autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 1992;20:140–143.
265. Milutinovic J, Fialkow PJ, Agodoa LY, et al. Clinical manifestations of autosomal dominant polycystic kidney disease in patients older than 50 years. *Am J Kidney Dis*. 1990;15:237–243.
266. Ubara Y, Katori H, Tagami T, et al. Transcatheter renal arterial embolization therapy on a patient with polycystic kidney disease on hemodialysis. *Am J Kidney Dis*. 1999;34:926–931.
267. Jones BE, Mkhaimer YG, Rangel LJ, et al. Asymptomatic pyuria as a prognostic biomarker in autosomal dominant polycystic kidney disease. *Kidney360*. 2022;3:465–476.
268. Anger J, Lee U, Ackerman AL, et al. Recurrent uncomplicated urinary tract infections in women: AUA/CUA/SUFU guideline. *J Urol*. 2019;202:282–289.
269. Lantinga MA, Darding AJ, de Sevaux RG, et al. International multi-specialty Delphi survey: identification of diagnostic criteria for hepatic and renal cyst infection. *Nephron*. 2016;134:205–214.
270. LeMaire SA, Zhang L, Zhang NS, et al. Ciprofloxacin accelerates aortic enlargement and promotes dissection and rupture in Marfan mice. *J Thorac Cardiovasc Surg*. 2022;163:e215–e226.
271. Son N, Choi E, Chung SY, et al. Risk of aortic aneurysm and aortic dissection with the use of fluoroquinolones in Korea: a nested case-control study. *BMC Cardiovasc Disord*. 2022;22:44.
272. Yu TM, Chuang YW, Yu MC, et al. Risk of cancer in patients with polycystic kidney disease: a propensity-score matched analysis of a nationwide, population-based cohort study. *Lancet Oncol*. 2016;17:1419–1425.
273. Wetmore JB, Calvet JP, Yu AS, et al. Polycystic kidney disease and cancer after renal transplantation. *J Am Soc Nephrol*. 2014;25:2335–2341.
274. Keith DS, Torres VE, King BF, et al. Renal cell carcinoma in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1994;4:1661–1669.
275. Kidney Disease: Improving Global Outcomes CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)*. 2017;7:1–59.
276. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2:279–335.
277. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl*. 2013;3:259–305.
278. Alam A, Perrone RD. Management of ESRD in patients with autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis*. 2010;17:164–172.
279. Buchholz B, Eckardt KU. Role of oxygen and the HIF-pathway in polycystic kidney disease. *Cell Signal*. 2020;69:109524.
280. Kraus A, Peters DJM, Klanke B, et al. HIF-1alpha promotes cyst progression in a mouse model of autosomal dominant polycystic kidney disease. *Kidney Int*. 2018;94:887–899.
281. Patel DM, Dahl NK. Examining the role of novel CKD therapies for the ADPKD patient. *Kidney360*. 2021;2:1036–1041.
282. Mariotti V, Fiorotto R, Cadamuro M, et al. New insights on the role of vascular endothelial growth factor in biliary pathophysiology. *JHEP Rep*. 2021;3:100251.
283. Ku E, Del Vecchio L, Eckardt KU, et al. Novel anemia therapies in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2023;104:655–680.

284. Akizawa T, Iwasaki M, Yamaguchi Y, et al. Phase 3, randomized, double-blind, active-comparator (darbepoetin alfa) study of oral roxadustat in CKD patients with anemia on hemodialysis in Japan. *J Am Soc Nephrol*. 2020;31:1628–1639.
285. Akizawa T, Iwasaki M, Yamaguchi Y, et al. Authors' reply. *J Am Soc Nephrol*. 2021;32:1005–1007.
286. ERBP Guideline Development Group on Vascular Access, Gatta G. [Linee guida di pratica clinica sulla cura peri- e post-operatoria delle fistole e delle protesi arterovenose per emodialisi negli adulti. Sintesi delle raccomandazioni delle "European Renal Best Practice (ERBP)"]. *G Ital Nefrol*. 2020;37(suppl 75):2020–S2075 [in Italian].
287. Reed B, Helal I, McFann K, et al. The impact of type II diabetes mellitus in patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2012;27:2862–2865.
288. Kraus A, Schley G, Kunzelmann K, et al. Glucose promotes secretion-dependent renal cyst growth. *J Mol Med (Berl)*. 2016;94:107–117.
289. Sas KM, Yin H, Fitzgibbon WR, et al. Hyperglycemia in the absence of cilia accelerates cystogenesis and induces renal damage. *Am J Physiol Renal Physiol*. 2015;309:F79–87.
290. Nowak KL, Hopp K. Metabolic reprogramming in autosomal dominant polycystic kidney disease: evidence and therapeutic potential. *Clin J Am Soc Nephrol*. 2020;15:577–584.
291. Kapoor S, Rodriguez D, Riwanto M, et al. Effect of sodium-glucose cotransport inhibition on polycystic kidney disease progression in PCK rats. *PLoS One*. 2015;10:e0125603.
292. Patel N, Hindi J, Farouk SS. Sodium-glucose cotransporter 2 inhibitors and kidney transplantation: What are we waiting for? *Kidney360*. 2021;2:1174–1178.
293. Blazer-Yost BL, Bacallao RL, Erickson BJ, et al. A randomized phase 1b cross-over study of the safety of low-dose pioglitazone for treatment of autosomal dominant polycystic kidney disease. *Clin Kidney J*. 2021;14:1738–1746.
294. Blazer-Yost BL, Haydon J, Eggleston-Gulyas T, et al. Pioglitazone attenuates cystic burden in the PCK rodent model of polycystic kidney disease. *PPAR Res*. 2010;2010:274376.
295. Muto S, Aiba A, Saito Y, et al. Pioglitazone improves the phenotype and molecular defects of a targeted Pkd1 mutant. *Hum Mol Genet*. 2002;11:1731–1742.
296. Nofziger C, Brown KK, Smith CD, et al. PPARgamma agonists inhibit vasopressin-mediated anion transport in the MDCK-C7 cell line. *Am J Physiol Renal Physiol*. 2009;297:F55–62.
297. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143.
298. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42:3227–3337.
299. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
300. Chapman AB, Devuyst O, Eckardt KU, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2015;88:17–27.
301. Perrone RD, Ruthazer R, Terrin NC. Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. *Am J Kidney Dis*. 2001;38:777–784.
302. Arjune S, Grundmann F, Todorova P, et al. Cardiac manifestations in patients with autosomal polycystic kidney disease (ADPKD)—a single-center study. *Kidney360*. 2023;4:150–161.
303. Bardaji A, Martinez-Vea A, Valero A, et al. Cardiac involvement in autosomal-dominant polycystic kidney disease: a hypertensive heart disease. *Clin Nephrol*. 2001;56:211–220.
304. Bouleti C, Flamant M, Escoubet B, et al. Risk of ascending aortic aneurysm in patients with autosomal dominant polycystic kidney disease. *Am J Cardiol*. 2019;123:482–488.
305. Hossack KF, Leddy CL, Johnson AM, et al. Echocardiographic findings in autosomal dominant polycystic kidney disease. *N Engl J Med*. 1988;319:907–912.
306. Lumiaho A, Ikaheimo R, Miettinen R, et al. Mitral valve prolapse and mitral regurgitation are common in patients with polycystic kidney disease type 1. *Am J Kidney Dis*. 2001;38:1208–1216.
307. Mange KC, Joffe MM, Feldman HI. Effect of the use or nonuse of long-term dialysis on the subsequent survival of renal transplants from living donors. *N Engl J Med*. 2001;344:726–731.
308. Cheungpasitporn W, Thongprayoon C, Vijayvargiya P, et al. The risk for new-onset diabetes mellitus after kidney transplantation in patients with autosomal dominant polycystic kidney disease: a systematic review and meta-analysis. *Can J Diabetes*. 2016;40:521–528.
309. Alasfar S, Hall IE, Mansour SG, et al. Contemporary incidence and risk factors of post-transplant erythrocytosis in deceased donor kidney transplantation. *BMC Nephrol*. 2021;22:26.
310. Alzoubi B, Kharel A, Machhi R, et al. Post-transplant erythrocytosis after kidney transplantation: a review. *World J Transplant*. 2021;11:220–230.
311. Jacquet A, Pallet N, Kessler M, et al. Outcomes of renal transplantation in patients with autosomal dominant polycystic kidney disease: a nationwide longitudinal study. *Transpl Int*. 2011;24:582–587.
312. Mekraksakit P, Boonpheng B, Leelaviwat N, et al. Risk factors and outcomes of post-transplant erythrocytosis among adult kidney transplant recipients: a systematic review and meta-analysis. *Transpl Int*. 2021;34:2071–2086.
313. Ronsin C, Chaba A, Suchanek O, et al. Incidence, risk factors and outcomes of kidney and liver cyst infection in kidney transplant recipient with ADPKD. *Kidney Int Rep*. 2022;7:867–875.
314. Chedid M, Kaidbay HD, Wigerinck S, et al. Cardiovascular outcomes in kidney transplant recipients with ADPKD. *Kidney Int Rep*. 2022;7:1991–2005.
315. Cheungpasitporn W, Thongprayoon C, Ungprasert P, et al. Subarachnoid hemorrhage in hospitalized renal transplant recipients with autosomal dominant polycystic kidney disease: a nationwide analysis. *J Clin Med*. 2019;8:524.
316. Hao X, Lai W, Xia X, et al. Skin cancer outcomes and risk factors in renal transplant recipients: analysis of organ procurement and transplantation network data from 2000 to 2021. *Front Oncol*. 2022;12:1017498.
317. Duarte-Chavez R, Stoltzfus J, Yellapu V, et al. Colonic diverticular disease in autosomal dominant polycystic kidney disease: Is there really an association? A nationwide analysis. *Int J Colorectal Dis*. 2021;36:83–91.
318. Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. *Transplantation*. 2020;104:S11–S103.
319. Meier-Kriesche HU, Port FK, Ojo AO, et al. Effect of waiting time on renal transplant outcome. *Kidney Int*. 2000;58:1311–1317.
320. Yoo SW, Kwon OJ, Kang CM. Preemptive living-donor renal transplantation: outcome and clinical advantages. *Transplant Proc*. 2009;41:117–120.
321. Lentine KL, Kasiske BL, Levey AS, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. *Transplantation*. 2017;101(8S suppl 1):S1–S109.
322. Basu A, Prieto M, Kosberg C, et al. Ten years of kidney paired donation at Mayo Clinic: the benefits of incorporating ABO/HLA compatible pairs. *Transplantation*. 2020;104:1229–1238.
323. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant*. 2009;9(suppl 3):S1–155.
324. Qian Q, Du H, King BF, et al. Sirolimus reduces polycystic liver volume in ADPKD patients. *J Am Soc Nephrol*. 2008;19:631–638.
325. Shillingford JM, Murcia NS, Larson CH, et al. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. *Proc Natl Acad Sci U S A*. 2006;103:5466–5471.
326. Veroux M, Zerbo D, Basile G, et al. Simultaneous native nephrectomy and kidney transplantation in patients with autosomal dominant polycystic kidney disease. *PLoS One*. 2016;11:e0155481.
327. Song WL, Zheng JM, Mo CB, et al. Kidney transplant for autosomal dominant polycystic kidney disease: the superiority of concurrent bilateral nephrectomy. *Urol Int*. 2011;87:54–58.
328. Pierre M, Moreau K, Braconnier A, et al. Unilateral nephrectomy versus renal arterial embolization and technique survival in peritoneal dialysis patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2020;35:320–327.
329. Jean RA, Alexandre M, Yoo PS. Kidney transplantation with and without native nephrectomy for polycystic kidney disease: results of the National Inpatient Sample and the rationale for a 2-staged procedure. *J Am Coll Surg*. 2018;226:1079–1084.
330. Jankowska M, Kuzmiuk-Glembin I, Skonieczny P, et al. Native nephrectomy in renal transplant recipients with autosomal dominant polycystic kidney disease. *Transplant Proc*. 2018;50:1863–1867.

331. Grodstein EI, Baggett N, Wayne S, et al. An evaluation of the safety and efficacy of simultaneous bilateral nephrectomy and renal transplantation for polycystic kidney disease: a 20-year experience. *Transplantation*. 2017;101:2774–2779.
332. Garcia-Rubio JH, Carrasco Valiente J, Campos Hernandez JP, et al. Graft survival in patients with polycystic kidney disease with nephrectomy of native kidney pretransplant. *Transplant Proc*. 2015;47:2615–2617.
333. Chebib FT, Prieto M, Jung Y, et al. Native nephrectomy in renal transplant recipients with autosomal dominant polycystic kidney disease. *Transplant Direct*. 2015;1:e43.
334. Ahmad SB, Inouye B, Phelan MS, et al. Live donor renal transplant with simultaneous bilateral nephrectomy for autosomal dominant polycystic kidney disease is feasible and satisfactory at long-term follow-up. *Transplantation*. 2016;100:407–415.
335. Abrol N, Bentall A, Torres VE, et al. Simultaneous bilateral laparoscopic nephrectomy with kidney transplantation in patients with ESRD due to ADPKD: a single-center experience. *Am J Transplant*. 2021;21:1513–1524.
336. Geertsema P, Gansevoort RT, Brenkman LPJ, et al. The impact of pre-transplantation nephrectomy on quality of life in patients with autosomal dominant polycystic kidney disease. *World J Urol*. 2023;41:1193–1203.
337. Jung Y, Irazabal MV, Chebib FT, et al. Volume regression of native polycystic kidneys after renal transplantation. *Nephrol Dial Transplant*. 2016;31:73–79.
338. Yamamoto T, Watarai Y, Kobayashi T, et al. Kidney volume changes in patients with autosomal dominant polycystic kidney disease after renal transplantation. *Transplantation*. 2012;93:794–798.
339. Xu J, D'Souza K, Lau NS, et al. Staged versus concurrent native nephrectomy and renal transplantation in patients with autosomal dominant polycystic kidney disease: a systematic review. *Transplant Rev (Orlando)*. 2022;36:100652.
340. Casteleijn NF, Geertsema P, Koorevaar IW, et al. The need for routine native nephrectomy in the workup for kidney transplantation in autosomal dominant polycystic kidney disease patients. *Urol Int*. 2023;107:148–156.
341. Maxeiner A, Bichmann A, Oberlander N, et al. Native nephrectomy before and after renal transplantation in patients with autosomal dominant polycystic kidney disease (ADPKD). *J Clin Med*. 2019;8:1622.
342. Rasmussen A, Levine MA, Mandurah MM, et al. Staged vs. simultaneous bilateral nephrectomy and kidney transplantation in patients with autosomal dominant polycystic kidney disease: outcomes and costs. *Can Urol Assoc J*. 2022;16:424–429.
343. Tyson MD, Wisenbaugh ES, Andrews PE, et al. Simultaneous kidney transplantation and bilateral native nephrectomy for polycystic kidney disease. *J Urol*. 2013;190:2170–2174.
344. Di Bello M, Di Bella C, Tuci F, et al. A large series of laparoscopic nephrectomies for polycystic kidneys pre, post and simultaneous with kidney transplantation: analysis of outcome. *Transpl Int*. 2021;34(suppl 1):72–73.
345. Eng M, Jones CM, Cannon RM, et al. Hand-assisted laparoscopic nephrectomy for polycystic kidney disease. *JSLS*. 2013;17:279–284.
346. Thomas MN, Datta RR, Wahba R, et al. Introduction of laparoscopic nephrectomy for autosomal dominant polycystic kidney disease as the standard procedure. *Langenbecks Arch Surg*. 2023;408:8.
347. Cornelis F, Couzi L, Le Bras Y, et al. Embolization of polycystic kidneys as an alternative to nephrectomy before renal transplantation: a pilot study. *Am J Transplant*. 2010;10:2363–2369.
348. Bonsib SM. Renal cystic diseases and renal neoplasms: a mini-review. *Clin J Am Soc Nephrol*. 2009;4:1998–2007.
349. Orskov B, Sorensen VR, Feldt-Rasmussen B, et al. Changes in causes of death and risk of cancer in Danish patients with autosomal dominant polycystic kidney disease and end-stage renal disease. *Nephrol Dial Transplant*. 2012;27:1607–1613.
350. Hajj P, Ferlicot S, Massoud W, et al. Prevalence of renal cell carcinoma in patients with autosomal dominant polycystic kidney disease and chronic renal failure. *Urology*. 2009;74:631–634.
351. Jilg CA, Drendel V, Bacher J, et al. Autosomal dominant polycystic kidney disease: prevalence of renal neoplasias in surgical kidney specimens. *Nephron Clin Pract*. 2013;123:13–21.
352. American College of Radiology Committee on Drugs and Contrast Media. ACR manual on contrast media 2024. Accessed August 2, 2023. https://www.acr.org/-/media/acr/files/clinical-resources/contrast_media.pdf
353. Expert Panel of Urologic Imaging, Wang ZJ, Nikolaidis P, et al. ACR appropriateness criteria indeterminate renal mass. *J Am Coll Radiol*. 2020;17(11S):S415–S428.
354. Davarpanah AH, Spektor M, Mathur M, et al. Homogeneous T1 hyperintense renal lesions with smooth borders: Is contrast-enhanced MR imaging needed? *Radiology*. 2016;280:128–136.
355. Kim CW, Shanbhogue KP, Schreiber-Zinaman J, et al. Visual assessment of the intensity and pattern of T1 hyperintensity on MRI to differentiate hemorrhagic renal cysts from renal cell carcinoma. *AJR Am J Roentgenol*. 2017;208:337–342.
356. Taouli B, Thakur RK, Mannelli L, et al. Renal lesions: characterization with diffusion-weighted imaging versus contrast-enhanced MR imaging. *Radiology*. 2009;251:398–407.
357. Chan CT, Blankestijn PJ, Dember LM, et al. Dialysis initiation, modality choice, access, and prescription: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;96:37–47.
358. Ma Y, Wang HY, Zhou ZJ, et al. Effectiveness of peritoneal dialysis in treating adult end stage renal disease patients with polycystic kidney disease. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2017;39:485–491.
359. Sigogne M, Kanagaratnam L, Dupont V, et al. Outcome of autosomal dominant polycystic kidney disease patients on peritoneal dialysis: a national retrospective study based on two French registries (the French Language Peritoneal Dialysis Registry and the French Renal Epidemiology and Information Network). *Nephrol Dial Transplant*. 2018;33:2020–2026.
360. Sigogne M, Kanagaratnam L, Mora C, et al. Identification of the factors associated with intraperitoneal pressure in ADPKD patients treated with peritoneal dialysis. *Kidney Int Rep*. 2020;5:1007–1013.
361. Yang JY, Chen L, Chao CT, et al. Comparative study of outcomes among patients with polycystic kidney disease on hemodialysis and peritoneal dialysis. *Sci Rep*. 2015;5:12816.
362. Janeiro D, Portoles J, Tato AM, et al. Peritoneal dialysis can be an option for dominant polycystic kidney disease: an observational study. *Perit Dial Int*. 2015;35:530–536.
363. Jankowska M, Chmielewski M, Lichodziejewska-Niemierko M, et al. Peritoneal dialysis as a treatment option in autosomal dominant polycystic kidney disease. *Int Urol Nephrol*. 2015;47:1739–1744.
364. Xie XS, Xie ZT, Xiang SL, et al. Peritoneal dialysis for autosomal dominant polycystic kidney disease: a retrospective study. *J Zhejiang Univ Sci B*. 2016;17:375–381.
365. Koc Y, Basturk T, Sakaci T, et al. Is peritoneal dialysis a therapeutic option for polycystic kidney disease? 15 years' experience in a single center. *Nephrol Ther*. 2016;12:215–220.
366. Kumar S, Fan SL, Raftery MJ, et al. Long-term outcome of patients with autosomal dominant polycystic kidney diseases receiving peritoneal dialysis. *Kidney Int*. 2008;74:946–951.
367. Kaul A, Dharshan R, Bhadhuaria D, et al. Is CAPD a viable option among ADPKD with end-stage renal disease population in India? Its outcomes and economics. *Saudi J Kidney Dis Transpl*. 2015;26:906–911.
368. Li L, Szeto CC, Kwan BC, et al. Peritoneal dialysis as the first-line renal replacement therapy in patients with autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 2011;57:903–907.
369. Lobbedez T, Touam M, Evans D, et al. Peritoneal dialysis in polycystic kidney disease patients. Report from the French peritoneal dialysis registry (RDPLF). *Nephrol Dial Transplant*. 2011;26:2332–2339.
370. Pandya BK, Friede T, Williams JD. A comparison of peritonitis in polycystic and non-polycystic patients on peritoneal dialysis. *Perit Dial Int*. 2004;24:79–81.
371. Yang JY, Chen L, Chao CT, et al. Outcome comparisons between patients on peritoneal dialysis with and without polycystic kidney disease: a nationwide matched cohort study. *Medicine (Baltimore)*. 2015;94:e2166.
372. Franco Palacios C, Keddis MT, Qin D, et al. Acute kidney injury in ADPKD patients with pneumonia. *Int J Nephrol*. 2011;2011:617904.
373. Patel V, Li L, Cobo-Stark P, et al. Acute kidney injury and aberrant planar cell polarity induce cyst formation in mice lacking renal cilia. *Hum Mol Genet*. 2008;17:1578–1590.
374. Mangoo-Karim R, Uchic M, Lechene C, et al. Renal epithelial cyst formation and enlargement *in vitro*: dependence on cAMP. *Proc Natl Acad Sci U S A*. 1989;86:6007–6011.
375. Wang X, Wu Y, Ward CJ, et al. Vasopressin directly regulates cyst growth in polycystic kidney disease. *J Am Soc Nephrol*. 2008;19:102–108.
376. Amro OW, Paulus JK, Noubary F, et al. Low-osmolar diet and adjusted water intake for vasopressin reduction in autosomal dominant

polycystic kidney disease: a pilot randomized controlled trial. *Am J Kidney Dis*. 2016;68:882–891.
377. McFarlane P, Parfrey P, Bichet D, et al. POS-337: Canadian real-world assesment of tolvaptan in ADPKD: C-major study and safety monitoring and distribution program. *Kidney Int Rep*. 2021;6:S146.
378. Thomas M, Gois PHF, Butcher BE, et al. Treatment persistence to tolvaptan in patients with autosomal dominant polycystic kidney disease: a secondary use of data analysis of patients in the IMADJIN(R) dataset. *BMC Nephrol*. 2021;22:400.
379. Choi HS, Han KD, Oh TR, et al. Trends in the incidence and prevalence of end-stage renal disease with hemodialysis in entire Korean population: a nationwide population-based study. *Medicine (Baltimore)*. 2021;100:e25293.
380. Chebib FT, Torres VE. Assessing risk of rapid progression in autosomal dominant polycystic kidney disease and special considerations for disease-modifying therapy. *Am J Kidney Dis*. 2021;78:282–292.
381. Fernando MR, Dent H, McDonald SP, et al. Incidence and survival of end-stage kidney disease due to polycystic kidney disease in Australia and New Zealand (1963-2014). *Popul Health Metr*. 2017;15:7.
382. Delanaye P, Glassock RJ, Pottel H, et al. An age-calibrated definition of chronic kidney disease: rationale and benefits. *Clin Biochem Rev*. 2016;37:17–26.
383. Greenberg A, Verbalis JG. Vasopressin receptor antagonists. *Kidney Int*. 2006;69:2124–2130.
384. Zhou X, Davenport E, Ouyang J, et al. Pooled data analysis of the long-term treatment effects of tolvaptan in ADPKD. *Kidney Int Rep*. 2022;7:1037–1048.
385. Edwards ME, Chebib FT, Irazabal MV, et al. Long-term administration of tolvaptan in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2018;13:1153–1161.
386. Estilo A, Tracy L, Matthews C, et al. Evaluating the impact of a risk evaluation and mitigation strategy with tolvaptan to monitor liver safety in patients with autosomal dominant polycystic kidney disease. *Clin Kidney J*. 2022;15:1553–1561.
387. Mekahli D, Guay-Woodford LM, Cadnapaphornchai MA, et al. Tolvaptan for children and adolescents with autosomal dominant polycystic kidney disease: randomized controlled trial. *Clin J Am Soc Nephrol*. 2023;18:36–46.
388. Torres VE, Chapman AB, Devuyst O, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 trial. *Nephrol Dial Transplant*. 2018;33:477–489.
389. Torres VE, Gansevoort RT, Perrone RD, et al. Tolvaptan in ADPKD patients with very low kidney function. *Kidney Int Rep*. 2021;6:2171–2178.
390. Casteleijn NF, Blais JD, Chapman AB, et al. Tolvaptan and kidney pain in patients with autosomal dominant polycystic kidney disease: secondary analysis from a randomized controlled trial. *Am J Kidney Dis*. 2017;69:210–219.
391. Irazabal MV, Blais JD, Perrone RD, et al. Prognostic enrichment design in clinical trials for autosomal dominant polycystic kidney disease: the TEMPO 3:4 clinical trial. *Kidney Int Rep*. 2016;1:213–220.
392. Spithoven EM, Kramer A, Meijer E, et al. Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease. *Kidney Int*. 2014;86:1244–1252.
393. Devuyst O, Chapman AB, Shoaf SE, et al. Tolerability of aquaretic-related symptoms following tolvaptan for autosomal dominant polycystic kidney disease: results from TEMPO 3:4. *Kidney Int Rep*. 2017;2:1132–1140.
394. Kramers BJ, Koorevaar IW, van Gastel MDA, et al. Effects of hydrochlorothiazide and metformin on aquaresis and nephroprotection by a vasopressin V2 receptor antagonist in ADPKD: a randomized crossover trial. *Clin J Am Soc Nephrol*. 2022;17:507–517.
395. Uchiyama K, Kitayama C, Yanai A, et al. The effect of trichlormethiazide in autosomal dominant polycystic kidney disease patients receiving tolvaptan: a randomized crossover controlled trial. *Sci Rep*. 2021;11:17666.
396. Akihisa T, Kataoka H, Makabe S, et al. Initial decline in eGFR to predict tolvaptan response in autosomal-dominant polycystic kidney disease. *Clin Exp Nephrol*. 2022;26:540–551.
397. Bellos I. Safety profile of tolvaptan in the treatment of autosomal dominant polycystic kidney disease. *Ther Clin Risk Manag*. 2021;17:649–656.
398. Torres VE, Chapman AB, Devuyst O, et al. Multicenter study of long-term safety of tolvaptan in later-stage autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2020;16:48–58.
399. Rodriguez-Espinosa D, Broseta JJ, Bastida C, et al. Creatine kinase elevation in autosomal dominant polycystic kidney disease patients on tolvaptan treatment. *Nephron*. 2022;147:152–157.
400. Parving HH, Hommel E, Jensen BR, et al. Long-term beneficial effect of ACE inhibition on diabetic nephropathy in normotensive type 1 diabetic patients. *Kidney Int*. 2001;60:228–234.
401. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
402. Chebib FT, Perrone RD, Chapman AB, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. *J Am Soc Nephrol*. 2018;29:2458–2470.
403. Mekahli D, Guay-Woodford L, Cadnaparphornchai M, et al. Randomized, placebo-controlled, phase 3b trial of tolvaptan in the treatment of children and adolescents with autosomal dominant polycystic kidney disease (ADPKD): 1-year data. *Nephrol Dial Transplant*. 2021;36(suppl 1):36–46.
404. Chan T, van der Merwe W, de Zoysa JR. Delay in funding of tolvaptan for polycystic kidney disease in Aotearoa New Zealand. *N Z Med J*. 2022;135:112–117.
405. Erickson KF, Chertow GM, Goldhaber-Fiebert JD. Cost-effectiveness of tolvaptan in autosomal dominant polycystic kidney disease. *Ann Intern Med*. 2013;159:382–389.
406. Chebib FT, Zhou X, Garbinsky D, et al. Tolvaptan and kidney function decline in older individuals with autosomal dominant polycystic kidney disease: a pooled analysis of randomized clinical trials and observational studies. *Kidney Med*. 2023;5:100639.
407. Perrone RD, Oberdhan D, Ouyang J, et al. OVERTURE: a worldwide, prospective, observational study of disease characteristics in patients with ADPKD. *Kidney Int Rep*. 2023;8:989–1001.
408. Bais T, Geertsema P, Knol MGE, et al. Validation of the Mayo Imaging Classification System for Predicting Kidney Outcomes in ADPKD. *Clin J Am Soc Nephrol*. 2024;19:591–601.
409. Bevilacqua M, Hague CJ, Romann A, et al. Accuracy, reproducibility and user experience with standardized instructions for measurement of total kidney volume in autosomal dominant polycystic kidney disease. *Can Assoc Radiol J*. 2023;74:343–350.
410. Bevilacqua MU, Hague CJ, Romann A, et al. CT of kidney volume in autosomal dominant polycystic kidney disease: accuracy, reproducibility, and radiation dose. *Radiology*. 2019;291:660–667.
411. Yoo J, Kim JU, Kim J, et al. Non-contrast low-dose CT can be used for volumetry of ADPKD. *BMC Nephrol*. 2023;24:317.
412. Brosnahan GM, Abebe KZ, Moore CG, et al. Patterns of kidney function decline in autosomal dominant polycystic kidney disease: a post hoc analysis from the HALT-PKD trials. *Am J Kidney Dis*. 2018;71:666–676.
413. Naranjo J, Borrego F, Rocha JL, et al. Real clinical experience after one year of treatment with tolvaptan in patients with autosomal dominant polycystic kidney disease. *Front Med (Lausanne)*. 2022;9:987092.
414. Shoaf SE, Ouyang J, Sergeyeva O, et al. A post hoc analysis of statin use in tolvaptan autosomal dominant polycystic kidney disease pivotal trials. *Clin J Am Soc Nephrol*. 2020;15:643–650.
415. Devuyst O, Torres VE. Osmoregulation, vasopressin, and cAMP signaling in autosomal dominant polycystic kidney disease. *Curr Opin Nephrol Hypertens*. 2013;22:459–470.
416. Devuyst O, Chapman AB, Gansevoort RT, et al. Urine osmolality, response to tolvaptan, and outcome in autosomal dominant polycystic kidney disease: results from the TEMPO 3:4 trial. *J Am Soc Nephrol*. 2017;28:1592–1602.
417. Gobburu J, Ivaturi V, Wang X, et al. Comparing effects of tolvaptan and instruction to increase water consumption in ADPKD: post hoc analysis of TEMPO 3:4. *Kidney360*. 2023;4:1702–1707.
418. Gansevoort RT, van Gastel MDA, Chapman AB, et al. Plasma copeptin levels predict disease progression and tolvaptan efficacy in autosomal dominant polycystic kidney disease. *Kidney Int*. 2019;96:159–169.
419. Oi A, Morishita K, Awogi T, et al. Nonclinical safety profile of tolvaptan. *Cardiovasc Drugs Ther*. 2011;25(suppl 1):S91–S99.
420. Alpers DH, Lewis JH, Hunt CM, et al. Clinical pattern of tolvaptan-associated liver injury in trial participants with autosomal dominant polycystic kidney disease (ADPKD): an analysis of pivotal clinical trials. *Am J Kidney Dis*. 2023;81:281–293.e1.
421. Kramers BJ, van Gastel MDA, Boertien WE, et al. Determinants of urine volume in ADPKD patients using the vasopressin V2 receptor antagonist tolvaptan. *Am J Kidney Dis*. 2019;73:354–362.

422. Watkins PB, Lewis JH, Kaplowitz N, et al. Clinical pattern of tolvaptan-associated liver injury in subjects with autosomal dominant polycystic kidney disease: analysis of clinical trials database. *Drug Saf*. 2015;38:1103–1113.
423. Endo M, Katayama K, Matsuo H, et al. Role of liver transplantation in tolvaptan-associated acute liver failure. *Kidney Int Rep*. 2019;4:1653–1657.
424. Zirngibl H, Mann S, Schild A, Zech M. Phospholipase A activities in ascites, serum, lymph, and urine in acute pancreatitis following pancreas stimulation with secretin-ceruletid. *Klin Wochenschr*. 1989;67:141–143.
425. Anderegg MA, Dhayat NA, Sommer G, et al. Quality of life in autosomal dominant polycystic kidney disease patients treated with tolvaptan. *Kidney Med*. 2020;2:162–171.
426. Harris PC, Torres VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. *J Clin Invest*. 2014;124:2315–2324.
427. Havard CW. Thiazide-induced antidiuresis in diabetes insipidus. *Proc R Soc Med*. 1965;58:1005–1007.
428. Efe O, Klein JD, LaRocque LM, et al. Metformin improves urine concentration in rodents with nephrogenic diabetes insipidus. *JCI Insight*. 2016;1:e88409.
429. Boertien WE, Meijer E, de Jong PE, et al. Short-term renal hemodynamic effects of tolvaptan in subjects with autosomal dominant polycystic kidney disease at various stages of chronic kidney disease. *Kidney Int*. 2013;84:1278–1286.
430. Irazabal MV, Huston J 3rd, Kubly V, et al. Extended follow-up of unruptured intracranial aneurysms detected by presymptomatic screening in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:1274–1285.
431. Uchiyama K, Honda K, Yoshida R, et al. Effect of tolvaptan in a patient with autosomal dominant polycystic kidney disease after living donor liver transplantation. *CEN Case Rep*. 2016;5:227–231.
432. El-Damanawi R, Harris T, Sandford RN, et al. Patient survey of current water intake practices in autosomal dominant polycystic kidney disease: the SIPs survey. *Clin Kidney J*. 2017;10:305–309.
433. Qaseem A, Dallas P, Forciea MA, et al. Dietary and pharmacologic management to prevent recurrent nephrolithiasis in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2014;161:659–667.
434. Wang CJ, Grantham JJ, Wetmore JB. The medicinal use of water in renal disease. *Kidney Int*. 2013;84:45–53.
435. Ho TA, Godefroid N, Gruzon D, et al. Autosomal dominant polycystic kidney disease is associated with central and nephrogenic defects in osmoregulation. *Kidney Int*. 2012;82:1121–1129.
436. Rangan GK, Dorani N, Zhang MM, et al. Clinical characteristics and outcomes of hyponatraemia associated with oral water intake in adults: a systematic review. *BMJ Open*. 2021;11:e046539.
437. El-Damanawi R, Lee M, Harris T, et al. Randomised controlled trial of high versus ad libitum water intake in patients with autosomal dominant polycystic kidney disease: rationale and design of the DRINK feasibility trial. *BMJ Open*. 2018;8:e022859.
438. Stout TE, Lingeman JE, Krambeck AE, et al. A randomized trial evaluating the use of a smart water bottle to increase fluid intake in stone formers. *J Ren Nutr*. 2022;32:389–395.
439. National Health and Medical Research Council (NHMRC). *Eat for Health: Australian Dietary Guidelines Summary*. NHMRC; 2013.
440. Campbell KL, Rangan GK, Lopez-Vargas P, Tong A. KHA-CARI autosomal dominant polycystic kidney disease guideline: diet and lifestyle management. *Semin Nephrol*. 2015;35:572–581.e17.
441. Chua TX, Prasad NS, Rangan GK, et al. A systematic review to determine the most effective interventions to increase water intake. *Nephrology (Carlton)*. 2016;21:860–869.
442. El-Damanawi R, Lee M, Harris T, et al. High water vs. ad libitum water intake for autosomal dominant polycystic kidney disease: a randomized controlled feasibility trial. *QJM*. 2020;113:258–265.
443. Sui Z, Zheng M, Zhang M, et al. Water and beverage consumption: analysis of the Australian 2011-2012 National Nutrition and Physical Activity Survey. *Nutrients*. 2016;8:678.
443a. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. *J Urol*. 2014;192:316.
444. Armstrong LE, Munoz CX, Armstrong EM. Distinguishing low and high water consumers-a paradigm of disease risk. *Nutrients*. 2020;12:858.
445. Travers S, Prot-Bertoye C, Daudon M, et al. How to monitor hydration status and urine dilution in patients with nephrolithiasis. *Nutrients*. 2023;15:1642.
446. Mannix C, Rangan A, Wong A, et al. Relative validity of a beverage frequency questionnaire used to assess fluid intake in the autosomal dominant polycystic kidney disease population. *Nutrients*. 2018;10:1051.
447. Ruggenenti P, Gentile G, Perico N, et al. Effect of sirolimus on disease progression in patients with autosomal dominant polycystic kidney disease and CKD stages 3b-4. *Clin J Am Soc Nephrol*. 2016;11:785–794.
448. Serra AL, Poster D, Kistler AD, et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. *N Engl J Med*. 2010;363:820–829.
449. Stallone G, Infante B, Grandaliano G, et al. Rapamycin for treatment of type I autosomal dominant polycystic kidney disease (RAPYD-study): a randomized, controlled study. *Nephrol Dial Transplant*. 2012;27:3560–3567.
450. Walz G, Budde K, Mannaa M, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2010;363:830–840.
451. Lin CH, Chao CT, Wu MY, et al. Use of mammalian target of rapamycin inhibitors in patient with autosomal dominant polycystic kidney disease: an updated meta-analysis. *Int Urol Nephrol*. 2019;51:2015–2025.
452. Kovarik JM, Hsu CH, McMahon L, et al. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. *Clin Pharmacol Ther*. 2001;70:247–254.
453. Torres VE, Boletta A, Chapman A, et al. Prospects for mTOR inhibitor use in patients with polycystic kidney disease and hamartomatous diseases. *Clin J Am Soc Nephrol*. 2010;5:1312–1329.
454. Anandh U, Chandrasekar G, Agarwal V. Mammalian target of rapamycin inhibitors in a patient with polycystic kidney disease-1-tuberous sclerosis-2 contiguous gene syndrome. *Saudi J Kidney Dis Transpl*. 2018;29:1475–1479.
455. Cabrera-Lopez C, Bullich G, Marti T, et al. Insight into response to mTOR inhibition when PKD1 and TSC2 are mutated. *BMC Med Genet*. 2015;16:39.
456. Pan X, Yang C, Ma S, et al. A case of TSC2-PKD1 contiguous deletion syndrome: clinical features and effective treatment for epilepsy. *Int J Dev Neurosci*. 2021;81:191–199.
457. Cadnapaphornchai MA, George DM, McFann K, et al. Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2014;9:889–896.
458. Fassett RG, Coombes JS, Packham D, et al. Effect of pravastatin on kidney function and urinary protein excretion in autosomal dominant polycystic kidney disease. *Scand J Urol Nephrol*. 2010;44:56–61.
459. Brosnahan GM, Abebe KZ, Rahbari-Oskoui FF, et al. Effect of statin therapy on the progression of autosomal dominant polycystic kidney disease. a secondary analysis of the HALT PKD trials. *Curr Hypertens Rev*. 2017;13:109–120.
460. Gimpel C, Bergmann C, Bockenhauer D, et al. International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. *Nat Rev Nephrol*. 2019;15:713–726.
461. Mallett A, Lee VW, Mai J, et al. KHA-CARI autosomal dominant polycystic kidney disease guideline: pharmacological management. *Semin Nephrol*. 2015;35:582–589.e17.
462. Brosnahan GM, Wang W, Gitomer B, et al. Metformin therapy in autosomal dominant polycystic kidney disease: a feasibility study. *Am J Kidney Dis*. 2022;79:518–526.
463. Chaudhary AR, Goswami M, Sen D, et al. POS-494: An open label randomized controlled study to evaluate the role of metformin to retard the progression of ADPKD. *Kidney Int Rep*. 2021;6:S213–S214.
464. Seliger SL, Abebe KZ, Hallows KR, et al. A randomized clinical trial of metformin to treat autosomal dominant polycystic kidney disease. *Am J Nephrol*. 2018;47:352–360.
465. Novelle MG, Ali A, Dieguez C, et al. Metformin: a hopeful promise in aging research. *Cold Spring Harb Perspect Med*. 2016;6:a025932.
466. Messchendorp AL, Casteleijn NF, Meijer E, et al. Somatostatin in renal physiology and autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2020;35:1306–1316.
467. Caroli A, Perico N, Perna A, et al. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet*. 2013;382:1485–1495.

468. Meijer E, Visser FW, van Aerts RMM, et al. Effect of lanreotide on kidney function in patients with autosomal dominant polycystic kidney disease: the DIPAK 1 randomized clinical trial. *JAMA*. 2018;320:2010–2019.
469. Perico N, Ruggenenti P, Perna A, et al. Octreotide-LAR in later-stage autosomal dominant polycystic kidney disease (ALADIN 2): a randomized, double-blind, placebo-controlled, multicenter trial. *PLoS Med*. 2019;16:e1002777.
470. van Aerts RMM, Kievit W, D'Agnolo HMA, et al. Lanreotide reduces liver growth in patients with autosomal dominant polycystic liver and kidney disease. *Gastroenterology*. 2019;157:481–491.e7.
471. van Keimpema L, Nevens F, Vanslembrouck R, et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. *Gastroenterology*. 2009;137:1661–1668.e1-2.
472. Hogan MC, Chamberlin JA, Vaughan LE, et al. Pansomatostatin agonist pasireotide long-acting release for patients with autosomal dominant polycystic kidney or liver disease with severe liver involvement: a randomized clinical trial. *Clin J Am Soc Nephrol*. 2020;15:1267–1278.
473. Lantinga MA, D'Agnolo HM, Casteleijn NF, et al. Hepatic cyst infection during use of the somatostatin analog lanreotide in autosomal dominant polycystic kidney disease: an interim analysis of the randomized open-label multicenter DIPAK-1 study. *Drug Saf*. 2017;40:153–167.
474. Aapkes SE, de Haas RJ, Bernts LHP, et al. Incident gallstones during somatostatin analog treatment are associated with acute biliary complications especially after discontinuation. *Drugs R D*. 2021;21:179–188.
475. Hogan MC, Masyuk TV, Page LJ, et al. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol*. 2010;21:1052–1061.
476. Hogan MC, Masyuk TV, Page L, et al. Somatostatin analog therapy for severe polycystic liver disease: results after 2 years. *Nephrol Dial Transplant*. 2012;27:3532–3539.
477. Pisani A, Sabbatini M, Imbriaco M, et al. Long-term effects of octreotide on liver volume in patients with polycystic kidney and liver disease. *Clin Gastroenterol Hepatol*. 2016;14:1022–1030.e4.
478. Suwabe T, Barrera FJ, Rodriguez-Gutierrez R, et al. Somatostatin analog therapy effectiveness on the progression of polycystic kidney and liver disease: a systematic review and meta-analysis of randomized clinical trials. *PLoS One*. 2021;16:e0257606.
479. Leonhard WN, Song X, Kanhai AA, et al. Salsalate, but not metformin or canagliflozin, slows kidney cyst growth in an adult-onset mouse model of polycystic kidney disease. *EBioMedicine*. 2019;47:436–445.
480. Rodriguez D, Kapoor S, Edenhofer I, et al. Inhibition of sodium-glucose cotransporter 2 with dapagliflozin in Han: SPRD rats with polycystic kidney disease. *Kidney Blood Press Res*. 2015;40:638–647.
481. Morioka F, Nakatani S, Uedono H, et al. Short-term dapagliflozin administration in autosomal dominant polycystic kidney disease-a retrospective single-arm case series study. *J Clin Med*. 2023;12:6341.
482. Nakatani S, Morioka F, Uedono H, et al. Dapagliflozin administration for 1 year promoted kidney enlargement in patient with ADPKD. *CEN Case Rep*. 2024;13:284–289.
483. Rowe I, Chiaravalli M, Mannella V, et al. Defective glucose metabolism in polycystic kidney disease identifies a new therapeutic strategy. *Nat Med*. 2013;19:488–493.
484. Kipp H, Kinne-Saffran E, Bevan C, Kinne RK. Characteristics of renal Na(+)-D-glucose cotransport in the skate (*Raja erinacea*) and shark (*Squalus acanthias*). *Am J Physiol*. 1997;273:R134–142.
485. Chebib FT, Nowak KL, Chonchol MB, et al. Polycystic kidney disease diet: what is known and what is safe. *Clin J Am Soc Nephrol*. 2023;19:664–682.
486. Ong ACM, Torra R. Can ketogenic dietary interventions slow disease progression in ADPKD: what we know and what we don't. *Clin Kidney J*. 2022;15:1034–1036.
487. Testa F, Marchio M, D'Amico R, et al. GREASE II. A phase II randomized, 12-month, parallel-group, superiority study to evaluate the efficacy of a Modified Atkins Diet in autosomal dominant polycystic kidney disease patients. *PharmaNutrition*. 2020;13:100206.
488. Strubl S, Oehm S, Torres JA, et al. Ketogenic dietary interventions in autosomal dominant polycystic kidney disease—a retrospective case series study: first insights into feasibility, safety and effects. *Clin Kidney J*. 2022;15:1079–1092.
489. Oehm S, Steinke K, Schmidt J, et al. RESET-PKD: a pilot trial on short-term ketogenic interventions in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2023;38:1623–1635.
490. Cukoski S, Lindemann CH, Arjune S, et al. Feasibility and impact of ketogenic dietary interventions in polycystic kidney disease: KETO-ADPKD—a randomized controlled trial. *Cell Rep Med*. 2023;4:101283.
491. Weimbs T, Saville J, Kalantar-Zadeh K. Ketogenic metabolic therapy for chronic kidney disease—the pro part. *Clin Kidney J*. 2024;17:sfad273.
492. Mahmoud SH, Ho-Huang E, Buhler J. Systematic review of ketogenic diet use in adult patients with status epilepticus. *Epilepsia Open*. 2020;5:10–21.
493. Acharya P, Acharya C, Thongprayoon C, et al. Incidence and characteristics of kidney stones in patients on ketogenic diet: a systematic review and meta-analysis. *Diseases*. 2021;9:39.
494. van Aerts RMM, van de Laarschot LFM, Banales JM, et al. Clinical management of polycystic liver disease. *J Hepatol*. 2018;68:827–837.
495. Hogan MC, Abebe K, Torres VE, et al. Liver involvement in early autosomal-dominant polycystic kidney disease. *Clin Gastroenterol Hepatol*. 2015;13:155–164.e6.
496. Reynolds DM, Falk CT, Li A, et al. Identification of a locus for autosomal dominant polycystic liver disease, on chromosome 19p13.2-13.1. *Am J Hum Genet*. 2000;67:1598–1604.
497. Suwabe T, Chamberlain AM, Killian JM, et al. Epidemiology of autosomal-dominant polycystic liver disease in Olmsted County. *JHEP Rep*. 2020;2:100166.
498. Bae KT, Zhu F, Chapman AB, et al. Magnetic resonance imaging evaluation of hepatic cysts in early autosomal-dominant polycystic kidney disease: the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease cohort. *Clin J Am Soc Nephrol*. 2006;1:64–69.
499. Kim H, Park HC, Ryu H, et al. Clinical correlates of mass effect in autosomal dominant polycystic kidney disease. *PLoS One*. 2015;10:e0144526.
500. Gigot JF, Legrand M, Hubens G, et al. Laparoscopic treatment of nonparasitic liver cysts: adequate selection of patients and surgical technique. *World J Surg*. 1996;20:556–561.
501. Schnelldorfer T, Torres VE, Zakaria S, et al. Polycystic liver disease: a critical appraisal of hepatic resection, cyst fenestration, and liver transplantation. *Ann Surg*. 2009;250:112–118.
502. Qian Q, Li A, King BF, et al. Clinical profile of autosomal dominant polycystic liver disease. *Hepatology*. 2003;37:164–171.
503. Neijenhuis MK, Kievit W, Verheesen SM, et al. Impact of liver volume on polycystic liver disease-related symptoms and quality of life. *United European Gastroenterol J*. 2018;6:81–88.
504. Bae KT, Tao C, Feldman R, et al. Volume progression and imaging classification of polycystic liver in early autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2022;17:374–384.
505. Sierks D, Schonauer R, Friedrich A, et al. Modelling polycystic liver disease progression using age-adjusted liver volumes and targeted mutational analysis. *JHEP Rep*. 2022;4:100579.
506. Chauveau D, Fakhouri F, Grunfeld JP. Liver involvement in autosomal-dominant polycystic kidney disease: therapeutic dilemma. *J Am Soc Nephrol*. 2000;11:1767–1775.
507. Barten TRM, Bokkerink RMP, Venderink W, et al. Abdominal wall hernia is a frequent complication of polycystic liver disease and associated with hepatomegaly. *Liver Int*. 2022;42:871–878.
508. European Association for the Study of the Liver. EASL clinical practice guidelines on management of cystic liver diseases. *J Hepatol*. 2022;77:1083–1108.
509. Van Keimpema L, De Koning DB, Van Hoek B, et al. Patients with isolated polycystic liver disease referred to liver centres: clinical characterization of 137 cases. *Liver Int*. 2011;31:92–98.
510. Gevers TJ, Nevens F, Torres VE, et al. Alkaline phosphatase predicts response in polycystic liver disease during somatostatin analogue therapy: a pooled analysis. *Liver Int*. 2016;36:595–602.
511. Wijnands TF, Neijenhuis MK, Kievit W, et al. Evaluating health-related quality of life in patients with polycystic liver disease and determining the impact of symptoms and liver volume. *Liver Int*. 2014;34:1578–1583.
512. Temmerman F, Dobbels F, Ho TA, et al. Development and validation of a polycystic liver disease complaint-specific assessment (POLCA). *J Hepatol*. 2014;61:1143–1150.
513. Neijenhuis MK, Gevers TJ, Hogan MC, et al. Development and validation of a disease-specific questionnaire to assess patient-reported symptoms in polycystic liver disease. *Hepatology*. 2016;64:151–160.
514. Neijenhuis MK, Wijnands TFM, Kievit W, et al. Symptom relief and not cyst reduction determines treatment success in aspiration sclerotherapy of hepatic cysts. *Eur Radiol*. 2019;29:3062–3068.
515. Bernts LHP, Echternach SG, Kievit W, et al. Clinical response after laparoscopic fenestration of symptomatic hepatic cysts: a systematic review and meta-analysis. *Surg Endosc*. 2019;33:691–704.

516. Aapkes SE, Bernts LHP, Barten TRM, et al. Estrogens in polycystic liver disease: a target for future therapies? *Liver Int*. 2021;41:2009–2019.
517. Chebib FT, Jung Y, Heyer CM, et al. Effect of genotype on the severity and volume progression of polycystic liver disease in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2016;31:952–960.
518. van Aerts RMM, Bernts LHP, Gevers TJG, et al. Estrogen-containing oral contraceptives are associated with polycystic liver disease severity in premenopausal patients. *Clin Pharmacol Ther*. 2019;106:1338–1345.
519. Sherstha R, McKinley C, Russ P, et al. Postmenopausal estrogen therapy selectively stimulates hepatic enlargement in women with autosomal dominant polycystic kidney disease. *Hepatology*. 1997;26:1282–1286.
520. Temmerman F, Ho TA, Vanslembrouck R, et al. Lanreotide reduces liver volume, but might not improve muscle wasting or weight loss, in patients with symptomatic polycystic liver disease. *Clin Gastroenterol Hepatol*. 2015;13:2353–2359.e1.
521. Mazzola A, Brustia R, Magro B, et al. Impact of sarcopenia on clinical outcomes of patients undergoing simultaneous liver and kidney transplantation: a cohort study. *Clin Res Hepatol Gastroenterol*. 2021;45:101692.
522. Jones DJ, Lal S, Strauss BJ, et al. Measurement of muscle mass and sarcopenia using anthropometry, bioelectrical impedance, and computed tomography in surgical patients with colorectal malignancy: comparison of agreement between methods. *Nutr Cancer*. 2020;72:1074–1083.
523. European Association for Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. *J Hepatol*. 2019;70:172–193.
524. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464–470.
525. Hamaguchi Y, Kaido T, Okumura S, et al. Proposal of Muscle-MELD Score, including muscularity, for prediction of mortality after living donor liver transplantation. *Transplantation*. 2016;100:2416–2423.
526. Chae MS, Moon KU, Jung JY, et al. Perioperative loss of psoas muscle is associated with patient survival in living donor liver transplantation. *Liver Transpl*. 2018;24:623–633.
527. van Vugt JL, Levolger S, de Bruin RW, et al. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. *Am J Transplant*. 2016;16:2277–2292.
528. D'Agnolo HM, Kievit W, van Munster KN, et al. Center is an important indicator for choice of invasive therapy in polycystic liver disease. *Transpl Int*. 2016;30:76–82.
529. Wijnands TF, Gortjes AP, Gevers TJ, et al. Efficacy and safety of aspiration sclerotherapy of simple hepatic cysts: a systematic review. *AJR Am J Roentgenol*. 2017;208:201–207.
530. Wijnands TF, Gevers TJ, Kool LJ, et al. Aspiration sclerotherapy combined with pasireotide to improve reduction of large symptomatic hepatic cysts (SCLEROCYST): study protocol for a randomized controlled trial. *Trials*. 2015;16:82.
531. Yan JY, Zhang JL, Yuan K, et al. Transarterial embolisation with bleomycin and N-butyl-2-cyanoacrylate -Lipiodol mixture for symptomatic polycystic liver disease: preliminary experience. *Clin Radiol*. 2019;74:975.e911–975.e916.
532. Coussy A, Jambon E, Le Bras Y, et al. The safety and efficacy of hepatic transarterial embolization using microspheres and microcoils in patients with symptomatic polycystic liver disease. *J Pers Med*. 2022;12:1624.
533. Boillot O, Cayot B, Guillaud O, et al. Partial major hepatectomy with cyst fenestration for polycystic liver disease: indications, short and long-term outcomes. *Clin Res Hepatol Gastroenterol*. 2021;45:101670.
534. Bernts LHP, Neijenhuis MK, Edwards ME, et al. Symptom relief and quality of life after combined partial hepatectomy and cyst fenestration in highly symptomatic polycystic liver disease. *Surgery*. 2020;168:25–32.
535. Chebib FT, Harmon A, Irazabal Mira MV, et al. Outcomes and durability of hepatic reduction after combined partial hepatectomy and cyst fenestration for massive polycystic liver disease. *J Am Coll Surg*. 2016;223:118–126.e1.
536. van Keimpema L, Nevens F, Adam R, et al. Excellent survival after liver transplantation for isolated polycystic liver disease: an European Liver Transplant Registry study. *Transpl Int*. 2011;24:1239–1245.
537. Gedaly R, Guidry P, Davenport D, et al. Peri-operative challenges and long-term outcomes in liver transplantation for polycystic liver disease. *HPB (Oxford)*. 2013;15:302–306.
538. Hogan MC, Masyuk TV, Page LJ, et al. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol*. 2010;21:1052–1061.
539. Pisani A, Sabbatini M, Imbriaco M, et al. Long-term effects of octreotide on liver volume in patients with polycystic kidney and liver disease. *Clin Gastroenterol Hepatol*. 2016;14:1022–1030.e1024.
540. Strasburger CJ, Karavitaki N, Stormann S, et al. Patient-reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly. *Eur J Endocrinol*. 2016;174:355–362.
541. Gevers TJ, Inthout J, Caroli A, et al. Young women with polycystic liver disease respond best to somatostatin analogues: a pooled analysis of individual patient data. *Gastroenterology*. 2013;145:357–365.e1–2.
542. Alpini G, Baiocchi L, Glaser S, et al. Ursodeoxycholate and tauroursodeoxycholate inhibit cholangiocyte growth and secretion of BDL rats through activation of PKC alpha. *Hepatology*. 2002;35:1041–1052.
543. D'Agnolo HM, Kievit W, Takkenberg RB, et al. Ursodeoxycholic acid in advanced polycystic liver disease: a phase 2 multicenter randomized controlled trial. *J Hepatol*. 2016;65:601–607.
544. Chrispijn M, Gevers TJ, Hol JC, et al. Everolimus does not further reduce polycystic liver volume when added to long acting octreotide: results from a randomized controlled trial. *J Hepatol*. 2013;59:153–159.
545. Mancinelli R, Franchitto A, Glaser S, et al. Vasopressin regulates the growth of the biliary epithelium in polycystic liver disease. *Lab Invest*. 2016;96:1147–1155.
546. Mizuno H, Hoshino J, Suwabe T, et al. Tolvaptan for the treatment of enlarged polycystic liver disease. *Case Rep Nephrol Dial*. 2017;7:108–111.
547. Torres VE, Higashihara E, Devuyst O, et al. Effect of tolvaptan in autosomal dominant polycystic kidney disease by CKD stage: results from the TEMPO 3:4 trial. *Clin J Am Soc Nephrol*. 2016;11:803–811.
548. NHS Blood and Transplant (NHSBT). Liver transplantation: selection criteria and recipient registration policy POL195/7. NHSBT; 2018. Accessed July 10, 2024. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/9440/pol195_7-liver-selection-policy.pdf
549. British Association for the Study of the Liver (BASL). *Guidelines for Referral for Liver Transplant Assessment*. BASL; 2012.
550. Organ Procurement and Transplantation Network. Guidance to liver transplant programs and the National Liver Review Board for: adult MELD exception review. Accessed August 2, 2023. https://optn.transplant.hrsa.gov/media/2847/liver_guidance_adult_meld_201706.pdf
551. Trevisol DJ, da Silva A, de Souza F, et al. Development and validation of a polycystic liver disease complaint-specific assessment (POLCA)—use of the Delphi technique for content validation. *J Hepatol*. 2015;62:988.
552. Kirchner GI, Rifai K, Cantz T, et al. Outcome and quality of life in patients with polycystic liver disease after liver or combined liver-kidney transplantation. *Liver Transpl*. 2006;12:1268–1277.
553. Coquillard C, Berger J, Daily M, et al. Combined liver-kidney transplantation for polycystic liver and kidney disease: analysis from the United Network for Organ Sharing dataset. *Liver Int*. 2016;36:1018–1025.
554. Simpson N, Cho YW, Cicciarelli JC, et al. Comparison of renal allograft outcomes in combined liver-kidney transplantation versus subsequent kidney transplantation in liver transplant recipients: analysis of UNOS Database. *Transplantation*. 2006;82:1298–1303.
555. Lantinga MA, Drenth JP, Gevers TJ. Diagnostic criteria in renal and hepatic cyst infection. *Nephrol Dial Transplant*. 2015;30:744–751.
556. Pijl JP, Glaudemans A, Slart R, et al. (18)F-FDG PET/CT in autosomal dominant polycystic kidney disease patients with suspected cyst infection. *J Nucl Med*. 2018;59:1734–1741.
557. Jouret F, Lhommel R, Devuyst O, et al. Diagnosis of cyst infection in patients with autosomal dominant polycystic kidney disease: attributes and limitations of the current modalities. *Nephrol Dial Transplant*. 2012;27:3746–3751.
558. Suwabe T, Ubara Y, Sumida K, et al. Clinical features of cyst infection and hemorrhage in ADPKD: new diagnostic criteria. *Clin Exp Nephrol*. 2012;16:892–902.
559. Yoshida H, Onda M, Tajiri T, et al. Intracystic hemorrhage of a simple hepatic cyst. *Hepatogastroenterology*. 2002;49:1095–1097.
560. Oh J, Shin CI, Kim SY. Infected cyst in patients with autosomal dominant polycystic kidney disease: analysis of computed tomographic and ultrasonographic imaging features. *PLoS One*. 2018;13:e0207880.
561. Suwabe T, Ubara Y, Ueno T, et al. Intracystic magnetic resonance imaging in patients with autosomal dominant polycystic kidney

disease: features of severe cyst infection in a case-control study. *BMC Nephrol*. 2016;17:170.
562. Suwabe T, Araoka H, Ubara Y, et al. Cyst infection in autosomal dominant polycystic kidney disease: causative microorganisms and susceptibility to lipid-soluble antibiotics. *Eur J Clin Microbiol Infect Dis*. 2015;34:1369–1379.
563. Telenti A, Torres VE, Gross JB Jr, et al. Hepatic cyst infection in autosomal dominant polycystic kidney disease. *Mayo Clin Proc*. 1990;65:933–942.
564. Lantinga MA, Wijnands TF, Te Morsche RH, et al. Hepatic cyst penetration of cefazolin in patients receiving aspiration sclerotherapy. *J Antimicrob Chemother*. 2016;71:2547–2552.
565. Hamanoue S, Suwabe T, Ubara Y, et al. Cyst infection in autosomal dominant polycystic kidney disease: penetration of meropenem into infected cysts. *BMC Nephrol*. 2018;19:272.
566. Elzinga LW, Golper TA, Rashad AL, et al. Trimethoprim-sulfamethoxazole in cyst fluid from autosomal dominant polycystic kidneys. *Kidney Int*. 1987;32:884–888.
567. Jouret F, Hogan MC, Chebib FT. A practical guide for the management of acute abdominal pain with fever in patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2022;37:1426–1428.
568. Lantinga MA, Geudens A, Gevers TJ, et al. Systematic review: the management of hepatic cyst infection. *Aliment Pharmacol Ther*. 2015;41:253–261.
569. Wijnands TF, Lantinga MA, Drenth JP. Hepatic cyst infection following aspiration sclerotherapy: a case series. *J Gastrointestin Liver Dis*. 2014;23:441–444.
570. National Institute for Health and Care Excellence (NICE). *Antimicrobials in Renal Impairment*. NICE Guideline [NG192]. NICE; 2022.
571. Sallee M, Rafat C, Zahar JR, et al. Cyst infections in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:1183–1189.
572. Belz MM, Hughes RL, Kaehny WD, et al. Familial clustering of ruptured intracranial aneurysms in autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 2001;38:770–776.
573. Flahault A, Trystram D, Nataf F, et al. Screening for intracranial aneurysms in autosomal dominant polycystic kidney disease is cost-effective. *Kidney Int*. 2018;93:716–726.
574. Kataoka H, Akagawa H, Yoshida R, et al. Impact of kidney function and kidney volume on intracranial aneurysms in patients with autosomal dominant polycystic kidney disease. *Sci Rep*. 2022;12:18056.
575. Lee CH, Ahn C, Ryu H, et al. Clinical factors associated with the risk of intracranial aneurysm rupture in autosomal dominant polycystic kidney disease. *Cerebrovasc Dis*. 2021;50:339–346.
576. Sanchis IM, Shukoor S, Irazabal MV, et al. Presymptomatic screening for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2019;14:1151–1160.
577. Xu HW, Yu SQ, Mei CL, et al. Screening for intracranial aneurysm in 355 patients with autosomal-dominant polycystic kidney disease. *Stroke*. 2011;42:204–206.
578. Vlak MH, Algra A, Brandenburg R, et al. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10:626–636.
579. Etminan N, Chang HS, Hackenberg K, et al. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure, and smoking prevalence in the population: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76:588–597.
580. Rinkel GJ, Ruigrok YM. Preventive screening for intracranial aneurysms. *Int J Stroke*. 2022;17:30–36.
581. Cho Y, Sautenet B, Gutman T, et al. Identifying patient-important outcomes in polycystic kidney disease: an international nominal group technique study. *Nephrology (Carlton,)*. 2019;24:1214–1224.
582. Yoshida H, Higashihara E, Maruyama K, et al. Relationship between intracranial aneurysms and the severity of autosomal dominant polycystic kidney disease. *Acta Neurochir (Wien)*. 2017;159:2325–2330.
583. Lefevre S, Audrezet MP, Halimi JM, et al. Diagnosis and risk factors for intracranial aneurysms in autosomal polycystic kidney disease: a cross-sectional study from the Genkyst cohort. *Nephrol Dial Transplant*. 2022;37:2223–2233.
584. Sung PH, Chiang HJ, Lee MS, et al. Combined renin-angiotensin-aldosterone system blockade and statin therapy effectively reduces the risk of cerebrovascular accident in autosomal dominant polycystic kidney disease: a nationwide population-based cohort study. *Oncotarget*. 2017;8:61570–61582.
585. Wilkinson DA, Burke JF, Nadel JL, et al. A large database analysis of rates of aneurysm screening, elective treatment, and subarachnoid hemorrhage in patients with polycystic kidney disease. *Neurosurgery*. 2019;85:E266–E274.
586. Cheungpasitporn W, Thongprayoon C, Ungprasert P, et al. Subarachnoid hemorrhage in hospitalized renal transplant recipients with autosomal dominant polycystic kidney disease: a nationwide analysis. *J Clin Med*. 2019;8:524.
587. Jiang T, Wang P, Qian Y, et al. A follow-up study of autosomal dominant polycystic kidney disease with intracranial aneurysms using 3.0 T three-dimensional time-of-flight magnetic resonance angiography. *Eur J Radiol*. 2013;82:1840–1845.
588. Schrier RW, Belz MM, Johnson AM, et al. Repeat imaging for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease with initially negative studies: a prospective ten-year follow-up. *J Am Soc Nephrol*. 2004;15:1023–1028.
589. Flahault A, Trystram D, Fouchard M, et al. Screening for unruptured intracranial aneurysms in autosomal dominant polycystic kidney disease: a survey of 420 nephrologists. *PLoS One*. 2016;11:e0153176.
590. Lefevre S, Audrezet MP, Halimi JM, et al. Diagnosis and risk factors for intracranial aneurysms in autosomal polycystic kidney disease: a cross-sectional study from the Genkyst cohort. *Nephrol Dial Transplant*. 2022;37:2223–2233.
591. Watnick T, Phakdeekitcharoen B, Johnson A, et al. Mutation detection of PKD1 identifies a novel mutation common to three families with aneurysms and/or very-early-onset disease. *Am J Hum Genet*. 1999;65:1561–1571.
592. Rossetti S, Chauveau D, Kubly V, et al. Association of mutation position in polycystic kidney disease 1 (PKD1) gene and development of a vascular phenotype. *Lancet*. 2003;361:2196–2201.
593. Teunissen LL, Rinkel GJ, Algra A, et al. Risk factors for subarachnoid hemorrhage: a systematic review. *Stroke*. 1996;27:544–549.
594. Korja M, Lehto H, Juvela S, et al. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. *Neurology*. 2016;87:1118–1123.
595. Iglesias CG, Torres VE, Offord KP, et al. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935-1980. *Am J Kidney Dis*. 1983;2:630–639.
596. Suwabe T, Shukoor S, Chamberlain AM, et al. Epidemiology of autosomal dominant polycystic kidney disease in Olmsted County. *Clin J Am Soc Nephrol*. 2019;15:69–79.
597. Greving JP, Wermer MJ, Brown RD Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014;13:59–66.
598. Morita A, Fujiwara S, Hashi K, et al. Risk of rupture associated with intact cerebral aneurysms in the Japanese population: a systematic review of the literature from Japan. *J Neurosurg*. 2005;102:601–606.
599. Wermer MJ, van der Schaaf IC, Algra A, et al. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. *Stroke*. 2007;38:1404–1410.
600. Matsuura R, Honda K, Oki R, et al. Screening and management for intracranial aneurysms in Japanese patients with ADPKD. *Kidney Int Rep*. 2022;7:1893–1896.
601. Wiebers DO, Whisnant JP, Huston J 3rd, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103–110.
602. UCAS Japan Investigators, Morita A, Kirino T, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med*. 2012;366:2474–2482.
603. Abulhasan YB, Alabdulraheem N, Simoneau G, et al. Mortality after spontaneous subarachnoid hemorrhage: causality and validation of a prediction model. *World Neurosurg*. 2018;112:e799–e811.
604. Mackey J, Khoury JC, Alwell K, et al. Stable incidence but declining case-fatality rates of subarachnoid hemorrhage in a population. *Neurology*. 2016;87:2192–2197.
605. Asikainen A, Korja M, Kaprio J, et al. Case fatality in patients with aneurysmal subarachnoid hemorrhage in Finland: a nationwide register-based study. *Neurology*. 2023;100:e348–e356.
606. Nurmonen HJ, Huttunen T, Huttunen J, et al. Lack of impact of polycystic kidney disease on the outcome of aneurysmal subarachnoid hemorrhage: a matched case-control study. *J Neurosurg*. 2020;134:1871–1878.
607. Algra AM, Lindgren A, Vergouwen MDI, et al. Procedural clinical complications, case-fatality risks, and risk factors in endovascular and

neurosurgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76:282–293.
608. Thompson BG, Brown RD Jr, Amin-Hanjani S, et al. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2368–2400.
609. Malhotra A, Wu X, Matouk CC, et al. MR angiography screening and surveillance for intracranial aneurysms in autosomal dominant polycystic kidney disease: a cost-effectiveness analysis. *Radiology*. 2019;291:400–408.
610. Walker EYX, Marlais M. Should we screen for intracranial aneurysms in children with autosomal dominant polycystic kidney disease? *Pediatr Nephrol*. 2022;38:77–85.
611. Chapman AB, Rubinstein D, Hughes R, et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. *N Engl J Med*. 1992;327:916–920.
612. Rozenfeld MN, Ansari SA, Mohan P, et al. Autosomal dominant polycystic kidney disease and intracranial aneurysms: Is there an increased risk of treatment? *AJNR Am J Neuroradiol*. 2016;37:290–293.
613. Yang ZL, Ni QQ, Schoepf UJ, et al. Small intracranial aneurysms: diagnostic accuracy of CT angiography. *Radiology*. 2017;285:941–952.
614. Sailer AM, Wagemans BA, Nelemans PJ, et al. Diagnosing intracranial aneurysms with MR angiography: systematic review and meta-analysis. *Stroke*. 2014;45:119–126.
615. Chen X, Liu Y, Tong H, et al. Meta-analysis of computed tomography angiography versus magnetic resonance angiography for intracranial aneurysm. *Medicine (Baltimore)*. 2018;97:e10771.
616. Schrier RW, Belz MM, Johnson AM, et al. Repeat imaging for intracranial aneurysms in patients with autosomal dominant polycystic kidney disease with initially negative studies: a prospective ten-year follow-up. *J Am Soc Nephrol*. 2004;15:1023–1028.
617. Zhou Z, Xu Y, Delcourt C, et al. Is regular screening for intracranial aneurysm necessary in patients with autosomal dominant polycystic kidney disease? A systematic review and meta-analysis. *Cerebrovasc Dis*. 2017;44:75–82.
618. Etminan N, de Sousa DA, Tiseo C, et al. European Stroke Organisation (ESO) guidelines on management of unruptured intracranial aneurysms. *Eur Stroke J*. 2022;7.
619. Perrone RD, Malek AM, Watnick T. Vascular complications in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol*. 2015;11:589–598.
620. Nunes R, Gouveia EMR, Almeida AG, et al. Does autosomal dominant polycystic kidney disease increase the risk of aortic aneurysm or dissection: a point of view based on a systematic review and meta-analysis. *J Nephrol*. 2022;35:1585–1593.
621. Grover P, Fitzgibbons TP. Spontaneous coronary artery dissection in a patient with autosomal dominant polycystic kidney disease: a case report. *J Med Case Rep*. 2016;10:62.
622. Itty CT, Farshid A, Talaulikar G. Spontaneous coronary artery dissection in a woman with polycystic kidney disease. *Am J Kidney Dis*. 2009;53:518–521.
623. Izumo T, Ogawa Y, Matsuo A, et al. A spontaneous extracranial internal carotid artery dissection with autosomal dominant polycystic kidney disease: a case report and literature review. *Medicina (Kaunas*. 2022;58:679.
624. Klingenberg-Salachova F, Limburg S, Boereboom F. Spontaneous coronary artery dissection in polycystic kidney disease. *Clin Kidney J*. 2012;5:44–46.
625. Kuroki T, Yamashiro K, Tanaka R, et al. Vertebral artery dissection in patients with autosomal dominant polycystic kidney disease. *J Stroke Cerebrovasc Dis*. 2014;23:e441–e443.
626. Larranaga J, Rutecki GW, Whittier FC. Spontaneous vertebral artery dissection as a complication of autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 1995;25:70–74.
627. Qian J, Lai Y, Kuang LJ, et al. Spontaneous coronary dissection should not be ignored in patients with chest pain in autosomal dominant polycystic kidney disease: a case report. *World J Clin Cases*. 2021;9:3095–3101.
628. Verlaeckt E, Van de Bruaene L, Coeman M, et al. Spontaneous coronary artery dissection in a patient with hereditary polycystic kidney disease and a recent liver transplant: a case report. *Eur Heart J Case Rep*. 2019;3:1–5.
629. Neves JB, Rodrigues FB, Lopes JA. Autosomal dominant polycystic kidney disease and coronary artery dissection or aneurysm: a systematic review. *Ren Fail*. 2016;38:493–502.
630. Torra R, Nicolau C, Badenas C, et al. Abdominal aortic aneurysms and autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1996;7:2483–2486.
631. Sung PH, Yang YH, Chiang HJ, et al. Risk of aortic aneurysm and dissection in patients with autosomal-dominant polycystic kidney disease: a nationwide population-based cohort study. *Oncotarget*. 2017;8:57594–57604.
632. Aoyagi S, Oda T, Kanamoto R, et al. Aortic dissection associated with autosomal dominant polycystic kidney disease. *Heart Surg Forum*. 2019;22:E032–E034.
633. Lee CC, Chang WT, Fang CC, et al. Sudden death caused by dissecting thoracic aortic aneurysm in a patient with autosomal dominant polycystic kidney disease. *Resuscitation*. 2004;63:93–96.
634. Menon A, Sachithanandan A, Singh H, et al. Simultaneous aortic valve and arch replacement with bilateral nephrectomy for massive polycystic kidney disease, aortic regurgitation and dissecting aneurysm. *Ann Thorac Surg*. 2011;91:919–920.
635. Silverio A, Prota C, Di Maio M, et al. Aortic dissection in patients with autosomal dominant polycystic kidney disease: a series of two cases and a review of the literature. *Nephrology (Carlton)*. 2015;20:229–235.
636. Biagini A, Maffei S, Baroni M, et al. Familiar clustering of aortic dissection in polycystic kidney disease. *Am J Cardiol*. 1993;72:741–742.
637. Inaba Y, Osako M, Aoki M, et al. Aortic dissection in familial patients with autosomal dominant polycystic kidney disease. *Ann Vasc Dis*. 2021;14:68–70.
638. Albornoz G, Coady MA, Roberts M, et al. Familial thoracic aortic aneurysms and dissections—incidence, modes of inheritance, and phenotypic patterns. *Ann Thorac Surg*. 2006;82:1400–1405.
639. Coady MA, Davies RR, Roberts M, et al. Familial patterns of thoracic aortic aneurysms. *Arch Surg*. 1999;134:361–367.
640. Howard DP, Banerjee A, Fairhead JF, et al. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. *Circulation*. 2013;127:2031–2037.
641. Gopalakrishnan C, Bykov K, Fischer MA, et al. Association of fluoroquinolones with the risk of aortic aneurysm or aortic dissection. *JAMA Intern Med*. 2020;180:1596–1605.
642. Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ*. 2018;360:k678.
643. Isselbacher EM, Preventza O, Hamilton Black Iii J, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;80:e223–e393.
644. Mancia G, Kreutz R, Brunstrom M, et al. 2023 ESH guidelines for the management of arterial hypertension, The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens*. 2023;41:1874–2071.
645. Leier CV, Baker PB, Kilman JW, et al. Cardiovascular abnormalities associated with adult polycystic kidney disease. *Ann Intern Med*. 1984;100:683–688.
646. Pfeferman MB, Rocha DRD, Rodrigues FG, et al. Echocardiographic abnormalities in autosomal dominant polycystic kidney disease (ADPKD) patients. *J Clin Med*. 2022;11:5982.
647. Savis A, Simpson JM, Kabir S, et al. Prevalence of cardiac valvar abnormalities in children and young people with autosomal dominant polycystic kidney disease. *Pediatr Nephrol*. 2022;38:705–709.
648. Chebib FT, Hogan MC, El-Zoghby ZM, et al. Autosomal dominant polycystic kidney patients may be predisposed to various cardiomyopathies. *Kidney Int Rep*. 2017;2:913–923.
649. Yu TM, Chuang YW, Yu MC, et al. New-onset atrial fibrillation is associated with polycystic kidney disease: a nationwide population-based cohort study. *Medicine (Baltimore)*. 2016;95:e2623.
650. Morris-Stiff G, Coles G, Moore R, et al. Abdominal wall hernia in autosomal dominant polycystic kidney disease. *Br J Surg*. 1997;84:615–617.
651. Mikolajczyk AE, Te HS, Chapman AB. Gastrointestinal manifestations of autosomal-dominant polycystic kidney disease. *Clin Gastroenterol Hepatol*. 2017;15:17–24.
652. Modi KB, Grant AC, Garret A, Rodger RS. Indirect inguinal hernia in CAPD patients with polycystic kidney disease. *Adv Perit Dial*. 1989;5:84–86.

653. Boonpheng B, Thongprayoon C, Wijarnpreecha K, et al. Outcomes of patients with autosomal-dominant polycystic kidney disease on peritoneal dialysis: a meta-analysis. *Nephrology (Carlton)*. 2019;24:638–646.
654. Schievink WI, Torres VE, Wiebers DO, et al. Intracranial arterial dolichoectasia in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1997;8:1298–1303.
655. Abderrahim E, Hedri H, Laabidi J, et al. Chronic subdural haematoma and autosomal polycystic kidney disease: report of two new cases. *Nephrology (Carlton)*. 2004;9:331–333.
656. Alehan FK, Gurakan B, Agildere M. Familial arachnoid cysts in association with autosomal dominant polycystic kidney disease. *Pediatrics*. 2002;110:e13.
657. Krauer F, Ahmadli U, Kollias S, et al. Growth of arachnoid cysts in patients with autosomal dominant polycystic kidney disease: serial imaging and clinical relevance. *Clin Kidney J*. 2012;5:405–411.
658. Schievink WI, Huston J 3rd, Torres VE, et al. Intracranial cysts in autosomal dominant polycystic kidney disease. *J Neurosurg*. 1995;83:1004–1007.
659. Wijdicks EF, Torres VE, Schievink WI. Chronic subdural hematoma in autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 2000;35:40–43.
660. Coche E, Persu A, Cosnard G, et al. Multiple thoracic paraspinal meningeal cysts in autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 2003;41:E8.
661. Peces R, Peces C, Perez-Duenas V, et al. Sacral radicular cysts in autosomal dominant polycystic kidney disease. *NDT Plus*. 2009;2:360–361.
662. Qian Q, Hartman RP, King BF, et al. Increased occurrence of pericardial effusion in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2007;2:1223–1227.
663. Dad T, Abebe KZ, Bae KT, et al. Longitudinal assessment of left ventricular mass in autosomal dominant polycystic kidney disease. *Kidney Int Rep*. 2018;3:619–624.
664. Perrone RD, Abebe KZ, Schrier RW, et al. Cardiac magnetic resonance assessment of left ventricular mass in autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:2508–2515.
665. Bataille S, Demoulin N, Devuyst O, et al. Association of PKD2 (polycystin 2) mutations with left-right laterality defects. *Am J Kidney Dis*. 2011;58:456–460.
666. Kumar S, Nanjappa B, Barapatre YR. Autosomal dominant polycystic kidney disease with situs inversus. *Urology*. 2012;80:e23–24.
667. Onoe T, Konoshita T, Tsuneyama K, et al. Situs inversus and cystic kidney disease: two adult patients with this heterogeneous syndrome. *Am J Case Rep*. 2013;14:20–25.
668. Qian Q, Younge BR, Torres VE. Retinal arterial and venous occlusions in patients with ADPKD. *Nephrol Dial Transplant*. 2007;22:1769–1771.
669. Kanaheswari Y, Hamzaini AH, Wong SW. Congenital hepatic fibrosis in a child with autosomal dominant polycystic kidney disease. *Med J Malaysia*. 2008;63:251–253.
670. O'Brien K, Font-Montgomery E, Lukose L, et al. Congenital hepatic fibrosis and portal hypertension in autosomal dominant polycystic kidney disease. *J Pediatr Gastroenterol Nutr*. 2012;54:83–89.
671. McNicholas BA, Kotaro Y, Martin W, et al. Pancreatic cysts and intraductal papillary mucinous neoplasm in autosomal dominant polycystic kidney disease. *Pancreas*. 2019;48:698–705.
672. Yin X, Prince WK, Blumenfeld JD, et al. Spleen phenotype in autosomal dominant polycystic kidney disease. *Clin Radiol*. 2019;74:975.e917–975.e924.
673. Ishikawa I, Chikamoto E, Nakamura M, et al. High incidence of common bile duct dilatation in autosomal dominant polycystic kidney disease patients. *Am J Kidney Dis*. 1996;27:321–326.
674. Kumar S, Adeva M, King BF, et al. Duodenal diverticulosis in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2006;21:3576–3578.
675. Driscoll JA, Bhalla S, Liapis H, et al. Autosomal dominant polycystic kidney disease is associated with an increased prevalence of radiographic bronchiectasis. *Chest*. 2008;133:1181–1188.
676. Moua T, Zand L, Hartman RP, et al. Radiologic and clinical bronchiectasis associated with autosomal dominant polycystic kidney disease. *PLoS One*. 2014;9:e93674.
677. Liu J, Yin X, Dev H, et al. Pleural effusions on MRI in autosomal dominant polycystic kidney disease. *J Clin Med*. 2023;12:386.
678. Torra R, Sarquella J, Calabia J, et al. Prevalence of cysts in seminal tract and abnormal semen parameters in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2008;3:790–793.
679. Belet U, Danaci M, Sarikaya S, et al. Prevalence of epididymal, seminal vesicle, prostate, and testicular cysts in autosomal dominant polycystic kidney disease. *Urology*. 2002;60:138–141.
680. Reig B, Blumenfeld J, Donahue S, et al. Seminal megavesicle in autosomal dominant polycystic kidney disease. *Clin Imaging*. 2015;39:289–292.
681. Alejmi A, Sayer JA. Multiple thyroid cysts as an extra-renal manifestation of ADPKD. *NDT Plus*. 2008;1:266–267.
682. Zalewska E, Kaniuka-Jakubowska S, Wisniewski P, et al. Incidence of thyroid nodules in early stage autosomal polycystic kidney disease. *BMC Nephrol*. 2022;23:85.
683. Joint World Health Organization (WHO)/Food and Agriculture Organization of the United Nations (FAO)/ and United Nations University (UNU) expert consultation. *Protein and Amino Acid Requirements in Human Nutrition. Technical Report Series*. WHO; 2007.
684. Torres VE, Grantham JJ, Chapman AB, et al. Potentially modifiable factors affecting the progression of autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:640–647.
685. Haring B, Selvin E, Liang M, et al. Dietary protein sources and risk for incident chronic kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) study. *J Ren Nutr*. 2017;27:233–242.
686. Nowak KL, Steele C, Gitomer B, et al. Overweight and obesity and progression of ADPKD. *Clin J Am Soc Nephrol*. 2021;16:908–915.
687. Fats and fatty acids in human nutrition. Report of an expert consultation. *FAO Food Nutr Pap*. 2010;91:1–166.
688. Hooper L, Abdelhamid A, Bunn D, et al. Effects of total fat intake on body weight. *Cochrane Database Syst Rev*. 2015;8:CD011834.
689. US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2020-2025. 9th ed*. US Government Printing Office; 2020.
690. Bach KE, Kelly JT, Palmer SC, et al. Healthy dietary patterns and incidence of CKD: a meta-analysis of cohort studies. *Clin J Am Soc Nephrol*. 2019;14:1441–1449.
691. Carriazo S, Perez-Gomez MV, Cordido A, et al. Dietary care for ADPKD patients: current status and future directions. *Nutrients*. 2019;11:1576.
692. World Health Organization. Health topics: alcohol. Accessed August 2, 2023. https://www.who.int/news-room/fact-sheets/detail/alcohol
693. Dion M, Ankawi G, Chew B, et al. CUA guideline on the evaluation and medical management of the kidney stone patient—2016 update. *Can Urol Assoc J*. 2016;10:E347–E358.
694. Malone PB, Coresh J, Greene T, et al. *Dietary Recommendations for Patients with Nondialysis Chronic Kidney Disease*. UpToDate; 2022.
695. Shrivastava SR, Shrivastava PS, Ramasamy J. World Health Organization advocates for a healthy diet for all: global perspective. *J Res Med Sci*. 2016;21:44.
696. Meijer E, Gansevoort RT. Emerging non-pharmacological interventions in ADPKD: an update on dietary advices for clinical practice. *Curr Opin Nephrol Hypertens*. 2021;30:482–492.
697. Geraghty RM, Davis NF, Tzelves L, et al. Best practice in interventional management of urolithiasis: an update from the European Association of Urology Guidelines Panel for Urolithiasis 2022. *Eur Urol Focus*. 2023;9:199–208.
698. Fick GM, Johnson AM, Hammond WS, et al. Causes of death in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1995;5:2048–2056.
699. Grubbs V, Lin F, Vittinghoff E, et al. Body mass index and early kidney function decline in young adults: a longitudinal analysis of the CARDIA (Coronary Artery Risk Development in Young Adults) study. *Am J Kidney Dis*. 2014;63:590–597.
700. Piche ME, Tchernof A, Despres JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res*. 2020;126:1477–1500.
701. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e984–e1010.
702. Chertow GM, Hsu CY, Johansen KL. The enlarging body of evidence: obesity and chronic kidney disease. *J Am Soc Nephrol*. 2006;17:1501–1502.
703. Franceschini N, Gouskova NA, Reiner AP, et al. Adiposity patterns and the risk for ESRD in postmenopausal women. *Clin J Am Soc Nephrol*. 2015;10:241–250.

704. Kambham N, Markowitz GS, Valeri AM, et al. Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int*. 2001;59:1498–1509.
705. Kataoka H, Ohara M, Shibui K, et al. Overweight and obesity accelerate the progression of IgA nephropathy: prognostic utility of a combination of BMI and histopathological parameters. *Clin Exp Nephrol*. 2012;16:706–712.
706. Kramer H, Gutierrez OM, Judd SE, et al. Waist circumference, body mass index, and ESRD in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. *Am J Kidney Dis*. 2016;67:62–69.
707. Kramer H, Luke A, Bidani A, et al. Obesity and prevalent and incident CKD: the Hypertension Detection and Follow-Up Program. *Am J Kidney Dis*. 2005;46:587–594.
708. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol*. 2005;16:2134–2140.
709. Silverwood RJ, Pierce M, Thomas C, et al. Association between younger age when first overweight and increased risk for CKD. *J Am Soc Nephrol*. 2013;24:813–821.
710. Yun HR, Kim H, Park JT, et al. Obesity, metabolic abnormality, and progression of CKD. *Am J Kidney Dis*. 2018;72:400–410.
711. Dos Santos Dutra A, Rodrigues FG, da Rocha DR, et al. Increased body fat and organic acid anions production are associated with larger kidney size in ADPKD. *Medicina (Kaunas)*. 2022;58:152.
712. Nowak KL, Murray K, You Z, et al. Pain and obesity in autosomal dominant polycystic kidney disease: a post hoc analysis of the Halt Progression of Polycystic Kidney Disease (HALT-PKD) studies. *Kidney Med*. 2021;3:536–545.e1.
713. Hopp K, Catenacci VA, Dwivedi N, et al. Weight loss and cystic disease progression in autosomal dominant polycystic kidney disease. *iScience*. 2022;25:103697.
714. Hanna RM, Ghobry L, Wassef O, et al. A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. *Blood Purif*. 2020;49:202–211.
715. Friedman AN, Schauer PR, Beddhu S, et al. Obstacles and opportunities in managing coexisting obesity and CKD: report of a scientific workshop cosponsored by the National Kidney Foundation and The Obesity Society. *Am J Kidney Dis*. 2022;80:783–793.
716. Kukla A, Diwan T, Smith BH, et al. Guiding kidney transplantation candidates for effective weight loss: a clinical cohort study. *Kidney360*. 2022;3:1411–1416.
717. Bakaj I, Pocai A. Metabolism-based approaches for autosomal dominant polycystic kidney disease. *Front Mol Biosci*. 2023;10:1126055.
718. Chintam K, Chang AR. Strategies to treat obesity in patients with CKD. *Am J Kidney Dis*. 2021;77:427–439.
719. Ryu H, Park HC, Kim H, et al. Bioelectrical impedance analysis as a nutritional assessment tool in autosomal dominant polycystic kidney disease. *PLoS One*. 2019;14:e0214912.
720. Franklin BA, Sallis RE, O'Connor FG. In: Fields KB, Grayzel J, eds. *Exercise prescription and guidance for adults*. UpToDate; 2022.
721. Montero-Odasso M, van der Velde N, Martin FC, et al. World guidelines for falls prevention and management for older adults: a global initiative. *Age Ageing*. 2022;51:afac20.
722. Delaney VB, Adler S, Bruns FJ, et al. Autosomal dominant polycystic kidney disease: presentation, complications, and prognosis. *Am J Kidney Dis*. 1985;5:104–111.
723. Deligiannis A, D'Alessandro C, Cupisti A. Exercise training in dialysis patients: impact on cardiovascular and skeletal muscle health. *Clin Kidney J*. 2021;14:ii25–ii33.
724. Epping-Jordan JE, Pruitt SD, Bengoa R, et al. Improving the quality of health care for chronic conditions. *Qual Saf Health Care*. 2004;13:299–305.
725. Brody JS, Wang W, Schrier RW, Reed-Gitomer B. Effects of smoking on ADPKD: frequency of vascular events and concentrations of soluble CD40 ligand. *Gen Med*. 2015;3:1000175.
726. Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005;36:2773–2780.
727. Yao X, Zhang K, Bian J, et al. Alcohol consumption and risk of subarachnoid hemorrhage: a meta-analysis of 14 observational studies. *Biomed Rep*. 2016;5:428–436.
728. US Food & Drug Administration. Spilling the beans: How much caffeine is too much? Accessed May 28, 2024. https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much
729. Rohweder R, de Oliveira Schmalfuss T, Dos Santos Borniger D, et al. Caffeine intake during pregnancy and adverse outcomes: an integrative review. *Reprod Toxicol*. 2024;123:108518.
730. Lakin H, Sheehan P, Soti V. Maternal caffeine consumption and its impact on the fetus: a review. *Cureus*. 2023;15:e48266.
731. Bhanushali GK, Jain G, Fatima H, et al. AKI associated with synthetic cannabinoids: a case series. *Clin J Am Soc Nephrol*. 2013;8:523–526.
732. Madhrira MM, Mohan S, Markowitz GS, et al. Acute bilateral renal infarction secondary to cocaine-induced vasospasm. *Kidney Int*. 2009;76:576–580.
733. Norris KC, Thornhill-Joynes M, Robinson C, et al. Cocaine use, hypertension, and end-stage renal disease. *Am J Kidney Dis*. 2001;38:523–528.
734. Goel N, Pullman JM, Coco M. Cocaine and kidney injury: a kaleidoscope of pathology. *Clin Kidney J*. 2014;7:513–517.
735. Davani-Davari D, Karimzadeh I, Khalili H. The potential effects of anabolic-androgenic steroids and growth hormone as commonly used sport supplements on the kidney: a systematic review. *BMC Nephrol*. 2019;20:198.
736. Longobardi I, Gualano B, Seguro AC, et al. Is it time for a requiem for creatine supplementation-induced kidney failure? A narrative review. *Nutrients*. 2023;15:1466.
737. Vlak MH, Rinkel GJ, Greebe P, et al. Lifetime risks for aneurysmal subarachnoid haemorrhage: multivariable risk stratification. *J Neurol Neurosurg Psychiatry*. 2013;84:619–623.
738. World Health Organization. Health topics: alcohol. Accessed August 2, 2023. https://www.who.int/news-room/fact-sheets/detail/alcohol
739. Vendramini LC, Nishiura JL, Baxmann AC, et al. Caffeine intake by patients with autosomal dominant polycystic kidney disease. *Braz J Med Biol Res*. 2012;45:834–840.
740. Mendoza MF, Sulague RM, Posas-Mendoza T, et al. Impact of coffee consumption on cardiovascular health. *Ochsner J*. 2023;23:152–158.
741. Buettner M, Toennes SW, Buettner S, et al. Nephropathy in illicit drug abusers: a postmortem analysis. *Am J Kidney Dis*. 2014;63:945–953.
742. Bundy JD, Bazzano LA, Xie D, et al. Self-reported tobacco, alcohol, and illicit drug use and progression of chronic kidney disease. *Clin J Am Soc Nephrol*. 2018;13:993–1001.
743. Nanavati A, Herlitz LC. Tubulointerstitial injury and drugs of abuse. *Adv Chronic Kidney Dis*. 2017;24:80–85.
744. Pendergraft WF 3rd, Herlitz LC, Thornley-Brown D, et al. Nephrotoxic effects of common and emerging drugs of abuse. *Clin J Am Soc Nephrol*. 2014;9:1996–2005.
745. Perneger TV, Klag MJ, Whelton PK. Recreational drug use: a neglected risk factor for end-stage renal disease. *Am J Kidney Dis*. 2001;38:49–56.
746. Seery C, Buchanan S. The psychosocial needs of patients who have chronic kidney disease without kidney replacement therapy: a thematic synthesis of seven qualitative studies. *J Nephrol*. 2022;35:2251–2267.
747. Tong A, Rangan GK, Ruospo M, et al. A painful inheritance-patient perspectives on living with polycystic kidney disease: thematic synthesis of qualitative research. *Nephrol Dial Transplant*. 2015;30:790–800.
748. Hedayati SS, Yalamanchili V, Finkelstein FO. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. *Kidney Int*. 2012;81:247–255.
749. Simms RJ, Thong KM, Dworschak GC, et al. Increased psychosocial risk, depression and reduced quality of life living with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2016;31:1130–1140.
750. Jankowska M, Walerzak A, Harciarek M, et al. Acceptance of illness, satisfaction with life, and emotional control in the early stage of autosomal dominant polycystic kidney disease. *Nephron*. 2022;148:1–6.
751. Sanon Aigbogun M, Oberdhan D, Doane MJ, et al. Disconnect in assessments of autosomal dominant polycystic kidney disease burden between patients and physicians: a survey study. *Int J Nephrol Renovasc Dis*. 2021;14:105–115.
752. Tong A, Mallett A, Lopez-Vargas P, et al. KHA-CARI autosomal dominant polycystic kidney disease guideline: psychosocial care. *Semin Nephrol*. 2015;35:590–594.e5.
753. Seery C, Buchanan S. The psychosocial needs of patients who have chronic kidney disease without kidney replacement therapy: a thematic synthesis of seven qualitative studies. *J Nephrol*. 2022;35:2251–2267.

754. Gittus M, Harris T, Ong AC. Patient perspectives on ADPKD. *Adv Kidney Dis Health*. 2023;30:294–302.
755. Logeman C, Cho Y, Sautenet B, et al. A sword of Damocles': patient and caregiver beliefs, attitudes and perspectives on presymptomatic testing for autosomal dominant polycystic kidney disease: a focus group study. *BMJ Open*. 2020;10:e038005.
756. Baker A, King D, Marsh J, et al. Understanding the physical and emotional impact of early-stage ADPKD: experiences and perspectives of patients and physicians. *Clin Kidney J*. 2015;8:531–537.
757. Delli Zotti GB, Sangiovanni E, Brioni E, et al. [Psychological assessment of a sample of women with ADPKD: quality of life, body image, anxiety and depression]. *G Ital Nefrol*. 2019;36:2019–vol2 [in Italian].
758. Quinn-Nilas C, Benson L, Milhausen RR, et al. The relationship between body image and domains of sexual functioning among heterosexual, emerging adult women. *Sex Med*. 2016;4:e182–189.
759. Holmes T, Chamberlin P, Young M. Relations of exercise to body image and sexual desirability among a sample of university students. *Psychol Rep*. 1994;74:920–922.
760. Faith MS, Schare ML. The role of body image in sexually avoidant behavior. *Arch Sex Behav*. 1993;22:345–356.
761. Andersen BL, Legrand J. Body image for women: conceptualization, assessment, and a test of its importance to sexual dysfunction and medical illness. *J Sex Res*. 1991;28:457–477.
762. Afshari P, Houshyar Z, Javadifar N, et al. The relationship between body image and sexual function in middle-aged women. *Electron Physician*. 2016;8:3302–3308.
763. Procci WR, Goldstein DA, Adelstein J, et al. Sexual dysfunction in the male patient with uremia: a reappraisal. *Kidney Int*. 1981;19:317–323.
764. Miller-Matero LR, Hecht LM, Miller MK, et al. A brief psychological intervention for chronic pain in primary care: a pilot randomized controlled trial. *Pain Med*. 2021;22:1603–1611.
765. Bevilacqua M, Gradin S, Williams J, et al. The BC ADPKD Network: a comprehensive provincial approach to support specialized and locally delivered multidisciplinary ADPKD care. *Can J Kidney Health Dis*. 2021;8:20543581211035218.
766. EAF Co-Chairs, Harris T, Sandford R, et al. European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care: European ADPKD Forum and Multispecialist Roundtable participants. *Nephrol Dial Transplant*. 2018;33:563–573.
767. Eriksson D, Karlsson L, Eklund O, et al. Real-world costs of autosomal dominant polycystic kidney disease in the Nordics. *BMC Health Serv Res*. 2017;17:560.
768. Brunelli SM, Blanchette CM, Claxton AJ, et al. End-stage renal disease in autosomal dominant polycystic kidney disease: a comparison of dialysis-related utilization and costs with other chronic kidney diseases. *Clinicoecon Outcomes Res*. 2015;7:65–72.
769. Alvaro D, Alpini G, Onori P, et al. Estrogens stimulate proliferation of intrahepatic biliary epithelium in rats. *Gastroenterology*. 2000;119:1681–1691.
770. Britton LE, Alspaugh A, Greene MZ, et al. CE: an evidence-based update on contraception. *Am J Nurs*. 2020;120:22–33.
771. Glaser S, DeMorrow S, Francis H, et al. Progesterone stimulates the proliferation of female and male cholangiocytes via autocrine/paracrine mechanisms. *Am J Physiol Gastrointest Liver Physiol*. 2008;295:G124–G136.
772. Qureshy Z, Lokken RP, Kakar S, et al. Influence of progestin-only hormonal use on hepatocellular adenomas: a retrospective cohort study. *Contraception*. 2022:109915.
773. Trussell J. Contraceptive failure in the United States. *Contraception*. 2011;83:397–404.
774. National Institute for Health and Care Excellence (NICE). Menopause: diagnosis and management. NICE guideline [NG23]. Accessed September 12, 2022. https://www.nice.org.uk/guidance/ng23
775. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100:3975–4011.
776. ESHRE PGT Consortium Steering Committee, Carvalho F, Coonen E, et al. ESHRE PGT Consortium good practice recommendations for the organisation of PGT. *Hum Reprod Open*. 2020;2020:hoaa021.
777. European Society of Human Reproduction and Embryology. Good practice recommendations for preimplantation genetic testing (PGT). Accessed September 1, 2022. https://www.eshre.eu/Guidelines-and-Legal/Guidelines/PGT
778. Snoek R, Stokman MF, Lichtenbelt KD, et al. Preimplantation genetic testing for monogenic kidney disease. *Clin J Am Soc Nephrol*. 2020;15:1279–1286.
779. Berckmoes V, Verdyck P, De Becker P, et al. Factors influencing the clinical outcome of preimplantation genetic testing for polycystic kidney disease. *Hum Reprod*. 2019;34:949–958.
780. Schreiber K, Frishman M, Russell MD, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice. *Rheumatology (Oxford)*. 2023;62:e89–e104.
781. Vora N, Perrone R, Bianchi DW. Reproductive issues for adults with autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 2008;51:307–318.
782. Wiles K, Chappell L, Clark K, et al. Clinical practice guideline on pregnancy and renal disease. *BMC Nephrol*. 2019;20:401.
783. Wiles K, Bramham K, Seed PT, et al. Serum creatinine in pregnancy: a systematic review. *Kidney Int Rep*. 2019;4:408–419.
784. US Preventative Services Task Force, Owens DK, Davidson KW, et al. Screening for asymptomatic bacteriuria in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2019;322:1188–1194.
785. Nicolle LE, Gupta K, Bradley SF, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2019;68:e83–e110.
786. Wu M, Wang D, Zand L, et al. Pregnancy outcomes in autosomal dominant polycystic kidney disease: a case-control study. *J Matern Fetal Neonatal Med*. 2016;29:807–812.
787. Eroglu E, Kocyigit I, Cetin M, et al. Multiple urinary tract infections are associated with genotype and phenotype in adult polycystic kidney disease. *Clin Exp Nephrol*. 2019;23:1188–1195.
788. Werter DE, Schneeberger C, Mol BWJ, et al. The risk of preterm birth in low risk pregnant women with urinary tract infections. *Am J Perinatol*. 2021;40:1558–1566.
789. Agrawal A, Wenger NK. Hypertension during pregnancy. *Curr Hypertens Rep*. 2020;22:64.
790. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. NICE guideline [NG133]. Accessed March 2, 2023. https://www.nice.org.uk/guidance/ng133
791. Tita AT, Szychowski JM, Boggess K, et al. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med*. 2022;386:1781–1792.
792. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension*. 2018;72:24–43.
793. Gestational hypertension and preeclampsia. ACOG practice bulletin, number 222. *Obstet Gynecol*. 2020;135:e237–e260.
794. Oliverio AL, Bramham K, Hladunewich MA. Pregnancy and CKD: advances in care and the legacy of Dr Susan Hou. *Am J Kidney Dis*. 2021;78:865–875.
795. Wiles K, Chappell LC, Lightstone L, et al. Updates in diagnosis and management of preeclampsia in women with CKD. *Clin J Am Soc Nephrol*. 2020;15:1371–1380.
796. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med*. 2016;374:13–22.
797. Rana S, Powe CE, Salahuddin S, et al. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation*. 2012;125:911–919.
798. Molina-Perez CJ, Nolasco-Leanos AG, Carrillo-Juarez RI, et al. Clinical usefulness of angiogenic factors in women with chronic kidney disease and suspected superimposed preeclampsia. *J Nephrol*. 2022;35:1699–1708.
799. Rolfo A, Attini R, Nuzzo AM, et al. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. *Kidney Int*. 2013;83:177–181.
800. de Jong MFC, Komdeur HM, Salih M, et al. Bleeding risk in patients with autosomal dominant polycystic kidney disease treated with acetylsalicylic acid: implications for prevention of preeclampsia. *J Nephrol*. 2022;35:2425–2427.
801. Boyer O, Gagnadoux MF, Guest G, et al. Prognosis of autosomal dominant polycystic kidney disease diagnosed in utero or at birth. *Pediatr Nephrol*. 2007;22:380–388.
802. Shamshirsaz AA, Reza Bekheirnia M, Kamgar M, et al. Autosomal-dominant polycystic kidney disease in infancy and childhood: progression and outcome. *Kidney Int*. 2005;68:2218–2224.

803. Nowak KL, Cadnapaphornchai MA, Chonchol MB, et al. Long-term outcomes in patients with very-early onset autosomal dominant polycystic kidney disease. *Am J Nephrol*. 2016;44:171–178.
804. Rossetti S, Hopp K, Sikkink RA, et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. *J Am Soc Nephrol*. 2012;23:915–933.
805. Waldrop E, Al-Obaide MAI, Vasylyeva TL. GANAB and PKD1 variations in a 12 years old female patient with early onset of autosomal dominant polycystic kidney disease. *Front Genet*. 2019;10:44.
806. Bergmann C. Early and severe polycystic kidney disease and related ciliopathies: an emerging field of interest. *Nephron*. 2019;141:50–60.
807. Youssef A, Fiorentini M, Di Donna G, et al. The correlation between transperineal ultrasound assessment of the levator ani muscle and postpartum urinary incontinence. *Neurourol Urodyn*. 2021;40:1786–1795.
808. Jia G, Jiang C, Wang K, et al. Epidemiological investigation of urinary incontinence in peri- and postpartum women from Nanjing, China. *Low Urin Tract Symptoms*. 2021;13:481–489.
809. Breysem L, De Keyzer F, Schellekens P, et al. Risk severity model for pediatric autosomal dominant polycystic kidney disease using 3D ultrasound volumetry. *Clin J Am Soc Nephrol*. 2023;18:581–591.
810. Mekahli D, Womack H, Dahl NK. Perspectives on drug development in early ADPKD. *Clin J Am Soc Nephrol*. 2022;17:1555–1558.
811. Grantham JJ. Rationale for early treatment of polycystic kidney disease. *Pediatr Nephrol*. 2015;30:1053–1062.
812. Cadnapaphornchai MA, Masoumi A, Strain JD, et al. Magnetic resonance imaging of kidney and cyst volume in children with ADPKD. *Clin J Am Soc Nephrol*. 2011;6:369–376.
813. De Rechter S, Bammens B, Schaefer F, et al. Unmet needs and challenges for follow-up and treatment of autosomal dominant polycystic kidney disease: the paediatric perspective. *Clin Kidney J*. 2018;11:i14–i26.
814. Fick GM, Johnson AM, Strain JD, et al. Characteristics of very early onset autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1993;3:1863–1870.
815. Fick-Brosnahan GM, Tran ZV, Johnson AM, et al. Progression of autosomal-dominant polycystic kidney disease in children. *Kidney Int*. 2001;59:1654–1662.
816. Reed B, Nobakht E, Dadgar S, et al. Renal ultrasonographic evaluation in children at risk of autosomal dominant polycystic kidney disease. *Am J Kidney Dis*. 2010;56:50–56.
817. Janssens P, Decuypere JP, De Rechter S, et al. Enhanced MCP-1 release in early autosomal dominant polycystic kidney disease. *Kidney Int Rep*. 2021;6:1687–1698.
818. Gimpel C, Bergmann C, Mekahli D. The wind of change in the management of autosomal dominant polycystic kidney disease in childhood. *Pediatr Nephrol*. 2022;37:473–487.
819. De Rechter S, Breysem L, Mekahli D. Is autosomal dominant polycystic kidney disease becoming a pediatric disorder? *Front Pediatr*. 2017;5:272.
820. Janssens P, Jouret F, Bammens B, et al. Implications of early diagnosis of autosomal dominant polycystic kidney disease: a post hoc analysis of the TEMPO 3:4 trial. *Sci Rep*. 2020;10:4294.
821. De Rechter S, Kringen J, Janssens P, et al. Clinicians' attitude towards family planning and timing of diagnosis in autosomal dominant polycystic kidney disease. *PLoS One*. 2017;12:e0185779.
822. Breysem L, De Rechter S, De Keyzer F, et al. 3DUS as an alternative to MRI for measuring renal volume in children with autosomal dominant polycystic kidney disease. *Pediatr Nephrol*. 2018;33:827–835.
823. Gimpel C, Avni FE, Bergmann C, et al. Perinatal diagnosis, management, and follow-up of cystic renal diseases: a clinical practice recommendation with systematic literature reviews. *JAMA Pediatr*. 2018;172:74–86.
824. Liebau MC, Serra AL. Looking at the (w)hole: magnet resonance imaging in polycystic kidney disease. *Pediatr Nephrol*. 2013;28:1771–1783.
825. McHugh K, Stringer DA, Hebert D, et al. Simple renal cysts in children: diagnosis and follow-up with US. *Radiology*. 1991;178:383–385.
826. Losekoot M, Haarloo C, Ruivenkamp C, et al. Analysis of missense variants in the PKHD1-gene in patients with autosomal recessive polycystic kidney disease (ARPKD). *Hum Genet*. 2005;118:185–206.
827. Halawi AA, Burgmaier K, Buescher AK, et al. Clinical characteristics and courses of patients with autosomal recessive polycystic kidney disease-mimicking phenocopies. *Kidney Int Rep*. 2023;8:1449–1454.
828. Fick GM, Duley IT, Johnson AM, et al. The spectrum of autosomal dominant polycystic kidney disease in children. *J Am Soc Nephrol*. 1994;4:1654–1660.
829. Marlais M, Cuthell O, Langan D, et al. Hypertension in autosomal dominant polycystic kidney disease: a meta-analysis. *Arch Dis Child*. 2016;101:1142–1147.
830. Massella L, Mekahli D, Paripovic D, et al. Prevalence of hypertension in children with early-stage ADPKD. *Clin J Am Soc Nephrol*. 2018;13:874–883.
831. Seeman T, Dusek J, Vondrichova H, et al. Ambulatory blood pressure correlates with renal volume and number of renal cysts in children with autosomal dominant polycystic kidney disease. *Blood Press Monit*. 2003;8:107–110.
832. Cadnapaphornchai MA, McFann K, Strain JD, et al. Increased left ventricular mass in children with autosomal dominant polycystic kidney disease and borderline hypertension. *Kidney Int*. 2008;74:1192–1196.
833. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140:e20171904.
834. ESCAPE Trial Group, Wuhl E, Trivelli A, et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med*. 2009;361:1639–1650.
835. Flynn JT, Urbina EM, Brady TM, et al. Ambulatory blood pressure monitoring in children and adolescents: 2022 update: a scientific statement from the American Heart Association. *Hypertension*. 2022;79:e114–e124.
836. Parati G, Stergiou G, O'Brien E, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens*. 2014;32:1359–1366.
837. Zeier M, Geberth S, Schmidt KG, et al. Elevated blood pressure profile and left ventricular mass in children and young adults with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 1993;3:1451–1457.
838. Cadnapaphornchai MA. Hypertension in children with autosomal dominant polycystic kidney disease (ADPKD). *Curr Hypertens Rev*. 2013;9:21–26.
839. Helal I, Reed B, McFann K, et al. Glomerular hyperfiltration and renal progression in children with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:2439–2443.
840. Wong H, Vivian L, Weiler G, et al. Patients with autosomal dominant polycystic kidney disease hyperfiltrate early in their disease. *Am J Kidney Dis*. 2004;43:624–628.
841. Burrello J, Erhardt EM, Saint-Hilary G, et al. Pharmacological treatment of arterial hypertension in children and adolescents: a network meta-analysis. *Hypertension*. 2018;72:306–313.
842. Hardy ST, Urbina EM. Blood pressure in childhood and adolescence. *Am J Hypertens*. 2021;34:242–249.
843. Klawitter J, McFann K, Pennington AT, et al. Pravastatin therapy and biomarker changes in children and young adults with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol*. 2015;10:1534–1541.
844. Yoon EY, Davis MM, Rocchini A, et al. Medical management of children with primary hypertension by pediatric subspecialists. *Pediatr Nephrol*. 2009;24:147–153.
845. Dachy A, Decuypere JP, Vennekens R, et al. Is autosomal dominant polycystic kidney disease an early sweet disease? *Pediatr Nephrol*. 2022;37:1945–1955.
846. Chedid M, Hanna C, Zaatari G, et al. Congenital heart disease in adults with autosomal dominant polycystic kidney disease. *Am J Nephrol*. 2022;53:316–324.
847. Mekahli D, Woolf AS, Bockenhauer D. Similar renal outcomes in children with ADPKD diagnosed by screening or presenting with symptoms. *Pediatr Nephrol*. 2010;25:2275–2282.
848. Ammenti A, Alberici I, Brugnara M, et al. Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. *Acta Paediatr*. 2020;109:236–247.
849. Subcommittee on Urinary Tract Infection. Reaffirmation of AAP clinical practice guideline: the diagnosis and management of the initial urinary tract infection in febrile infants and young children 2-24 months of age. *Pediatrics*. 2016;138:e20163026.
850. 't Hoen LA, Bogaert G, Radmayr C, et al. Update of the EAU/ESPU guidelines on urinary tract infections in children. *J Pediatr Urol*. 2021;17:200–207.
851. Furth SL, Pierce C, Hui WF, et al. Estimating time to ESRD in children with CKD. *Am J Kidney Dis*. 2018;71:783–792.

852. Neveus T, Fonseca E, Franco I, et al. Management and treatment of nocturnal enuresis—an updated standardization document from the International Children's Continence Society. *J Pediatr Urol*. 2020;16:10–19.
853. Gimpel C, Avni EF, Breysem L, et al. Imaging of kidney cysts and cystic kidney diseases in children: an international working group consensus statement. *Radiology*. 2019;290:769–782.
854. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med*. 2007;357:2329–2337.
855. Franks PW, Hanson RL, Knowler WC, et al. Childhood obesity, other cardiovascular risk factors, and premature death. *N Engl J Med*. 2010;362:485–493.
856. Kovesdy CP, Furth SL, Zoccali C, et al. Obesity and kidney disease: hidden consequences of the epidemic. *J Nephrol*. 2017;30:1–10.
857. KDOQI Work Group. KDOQI Clinical Practice Guideline For Nutrition In Children with CKD: 2008 update. Executive summary. *Am J Kidney Dis*. 2009;53:S11–104.
858. Watson AR, Harden P, Ferris M, et al. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). *Pediatr Nephrol*. 2011;26:1753–1757.
859. Watson AR, Harden PN, Ferris ME, et al. Transition from pediatric to adult renal services: a consensus statement by the International Society of Nephrology (ISN) and the International Pediatric Nephrology Association (IPNA). *Kidney Int*. 2011;80:704–707.
860. Wildes DM, Costigan CS, Kinlough M, et al. Transitional care models in adolescent kidney transplant recipients—a systematic review. *Nephrol Dial Transplant*. 2022;38:49–55.
861. Nishi L, Langman C, Ghossein C. A nephrology pediatric to adult transition clinic: a pilot program. *Kidney Med*. 2019;1:405–406.
862. Muller RU, Benzing T. Cystic kidney diseases from the adult nephrologist's point of view. *Front Pediatr*. 2018;6:65.
863. Hattori M, Iwano M, Sako M, et al. Transition of adolescent and young adult patients with childhood-onset chronic kidney disease from pediatric to adult renal services: a nationwide survey in Japan. *Clin Exp Nephrol*. 2016;20:918–925.
864. Kreuzer M, Drube J, Prufe J, et al. Current management of transition of young people affected by rare renal conditions in the ERKNet. *Eur J Hum Genet*. 2019;27:1783–1790.
865. Janssens P, Weydert C, De Rechter S, et al. Expanding the role of vasopressin antagonism in polycystic kidney diseases: from adults to children? *Pediatr Nephrol*. 2018;33:395–408.
866. Schaefer F, Mekahli D, Emma F, et al. Tolvaptan use in children and adolescents with autosomal dominant polycystic kidney disease: rationale and design of a two-part, randomized, double-blind, placebo-controlled trial. *Eur J Pediatr*. 2019;178:1013–1021.
867. Nowak KL, Farmer-Bailey H, Wang W, et al. Curcumin therapy to treat vascular dysfunction in children and young adults with ADPKD: a randomized controlled trial. *Clin J Am Soc Nephrol*. 2022;17:240–250.
868. National Institute for Health and Care Excellence (NICE). Shared decision making. NICE guideline [NG197]. Accessed July 10, 2024. https://www.nice.org.uk/guidance/ng197
869. Elwyn G, Laitner S, Coulter A, et al. Implementing shared decision making in the NHS. *BMJ*. 2010;341:c5146.
870. Lawal AK, Rotter T, Kinsman L, et al. What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic review. *BMC Med*. 2016;14:35.
871. Rotter T, Kinsman L, James E, et al. The quality of the evidence base for clinical pathway effectiveness: room for improvement in the design of evaluation trials. *BMC Med Res Methodol*. 2012;12:80.
872. Ayme S, Bockenhauer D, Day S, et al. Common elements in rare kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2017;92:796–808.
873. Shen H, van der Kleij R, van der Boog PJM, et al. Electronic health self-management interventions for patients with chronic kidney disease: systematic review of quantitative and qualitative evidence. *J Med Internet Res*. 2019;21:e12384.
874. Mao Z, Chong J, Ong AC. Autosomal dominant polycystic kidney disease: recent advances in clinical management. *F1000Res*. 2016;5:2029.
875. Ong AC, Devuyst O, Knebelmann B, et al. Autosomal dominant polycystic kidney disease: the changing face of clinical management. *Lancet*. 2015;385:1993–2002.
876. Sautenet B, Cho Y, Gutman T, et al. Range and variability of outcomes reported in randomized trials conducted in patients with polycystic kidney disease: a systematic review. *Am J Kidney Dis*. 2020;76:213–223.
877. Cho Y, Tong A, Craig JC, et al. Establishing a core outcome set for autosomal dominant polycystic kidney disease: report of the Standardized Outcomes in Nephrology-Polycystic Kidney Disease (SONG-PKD) Consensus Workshop. *Am J Kidney Dis*. 2021;77:255–263.
878. Herrington WG, Staplin N, Haynes R. Kidney disease trials for the 21st century: innovations in design and conduct. *Nat Rev Nephrol*. 2020;16:173–185.
879. Kotwal S, Perkovic V, Heerspink HJL. Platform clinical trials within nephrology—interpreting the evidence. *Am J Kidney Dis*. 2022;80:143–146.
880. Nestor JG. Assessing physician needs for the implementation of personalized care. *Kidney Int Rep*. 2021;6:243–245.
881. Tumiene B, Graessner H. Rare disease care pathways in the EU: from odysseys and labyrinths towards highways. *J Community Genet*. 2021;12:231–239.
882. Morris S, Hudson E, Bloom L, et al. Co-ordinated care for people affected by rare diseases: the CONCORD mixed-methods study. *Health Social Care Deliv Res*. 2022;10(5). https://doi.org/10.3310/LNZZ5321
883. Winterbottom J, Simms RJ, Caroli A, et al. Flank pain has a significant adverse impact on quality of life in ADPKD: the CYSTic-QoL study. *Clin Kidney J*. 2022;15:2063–2071.
884. Allegrante JP, Wells MT, Peterson JC. Interventions to support behavioral self-management of chronic diseases. *Annu Rev Public Health*. 2019;40:127–146.
885. Warsi A, Wang PS, LaValley MP, et al. Self-management education programs in chronic disease: a systematic review and methodological critique of the literature. *Arch Intern Med*. 2004;164:1641–1649.
886. Lightfoot CJ, Nair D, Bennett PN, et al. Patient activation: the cornerstone of effective self-management in chronic kidney disease? *Kidney Dial*. 2022;2:91–105.
887. Perrone RD, Neville J, Chapman AB, et al. Therapeutic area data standards for autosomal dominant polycystic kidney disease: a report from the Polycystic Kidney Disease Outcomes Consortium (PKDOC). *Am J Kidney Dis*. 2015;66:583–590.
888. Institute of Medicine (US). *Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. Finding What Works in Health Care: Standards for Systematic Reviews*. National Academies; 2011.
889. Institute of Medicine (US). Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R, Mancher M, Miller Wolman DW, et al., eds. *Clinical Practice Guidelines We Can Trust*. National Academies; 2011.
890. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *J Clin Epidemiol*. 2010;63:1308–1311.
891. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the *Journal of Clinical Epidemiology*. *J Clin Epidemiol*. 2011;64:380–382.
892. Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Wiley; 2019.
893. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015;68:1312–1324.
894. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–926.
895. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
896. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
897. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) resource [Internet]. Food and Drug Administration (US). Accessed July 10, 2024. https://www.ncbi.nlm.nih.gov/books/NBK326791. Co-published by National Institutes of Health (US).
898. EIT Health. *Implementing Value-Based Health Care in Europe: Handbook for Pioneers*. Katz G, ed. Publications Office of the European Union; 2020.
899. McKenna SP, Heaney A, Wilburn J, et al. Measurement of patient-reported outcomes. 1: The search for the Holy Grail. *J Med Econ*. 2019;22:516–522.

Appendix 1: Patient-reported outcome measures (PROMs) in ADPKD care

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 healthcare provider or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response".[897]

PROMs are validated surveys administered by various means (e.g., paper, online), and the patient may be asked to complete these before, during, or after a clinic appointment, or after treatment and/or interventions. PROMs can be collected at several points in 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 people 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 person with CKD,
- 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),

Appendix Table 1 | List of suggested patient-reported outcome measures (PROMs) appropriate for people with autosomal dominant polycystic kidney disease (ADPKD)

PRO	PROM	Note	Link (usage licenses may be needed)
ADPKD-specific			
ADPKD HRQOL	ADPKD-IS	Needs more validation and qualification	ePROVIDE: https://eprovide.mapi-trust.org/instruments/autosomal-dominant-polycystic-kidney-disease-impact-scale National Kidney Foundation: https://doi.org/10.1053/j.ajkd.2017.08.020
ADPKD Pain	ADPKD-PDS	Needs more validation and qualification	ePROVIDE: https://eprovide.mapi-trust.org/instruments/autosomal-dominant-polycystic-kidney-disease-pain-and-discomfort-scale
	APAT	Single-center questionnaire developed to facilitate research. Not validated.	https://pubmed.ncbi.nlm.nih.gov/34754429/
ADPKD Urinary Output	ADPKD-UIS	Needs more validation	ePROVIDE: https://eprovide.mapi-trust.org/instruments/autosomal-dominant-polycystic-kidney-disease-urinary-impact-scale
ADPKD Genetic Psychosocial Risk Instrument	ADPKD-GPRI	Single center validated GPRI modified to specifically explore the psychosocial impact of coping with a diagnosis of ADPKD	https://academic.oup.com/ndt/article/31/7/1130/1751693
Polycystic Liver Disease Symptom Frequency and Discomfort	PLD-Q	Has been accepted within the process of the FDA COA Qualification Program for use as a drug development tool for the purpose of regulatory decision-making	ePROVIDE: https://eprovide.mapi-trust.org/instruments/polycystic-liver-disease-questionnaire
Polycystic Liver Disease Complaint-specific Assessment	POLCA	Self-report instrument to capture the presence and severity of disease specific complaints for polycystic liver disease.	No information
CKD			
Generic QOL	WHOQOL-100 or WHOQOL-BREF	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 WHO QOL lists 6 domains with 24 facets which cover: physical, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs.	World Health Organization: https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03

Appendix Table 1 | (Continued)

PRO	PROM	Note	Link (usage licenses may be needed)
Generic CKD HRQOL – ICHOM Set of Patient-Centered Outcome Measures for Chronic Kidney Disease	• SF-36v2 or SF-12v2 • RAND-36 (distributed by RAND) • PROMIS Global Health + PROMIS-29	The ICHOM developed an "International Standard Set of Value-Based Outcome Measures for Patients with CKD" which includes PROMs.[26] 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. Recent examples of the use of SF-36v2, SF-12v2 and RAND-36 in ADPKD are listed.	Quality Metric: https://www.qualitymetric.com/health-surveys/the-sf-36v2-health-survey/ https://doi.org/10.1093/ckj/sfac144 https://doi.org/10.1016/j.ekir.2023.02.1073 RAND: https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html PROMIS: https://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures
Kidney Transplant	KTQ-25	Developed to assess the QoL of kidney transplant recipients	ePROVIDE: https://eprovide.mapi-trust.org/instruments/kidney-transplant-questionnaire-25-items
Anxiety	GAD-7	Widely used to identify probable cases of generalized anxiety disorder and assess symptom severity in generalized anxiety disorder	ePROVIDE: https://eprovide.mapi-trust.org/instruments/generalized-anxiety-disorder-7
Depression severity	BDI®-II	Widely used to measure the severity of depression in adults and adolescents	ePROVIDE: https://eprovide.mapi-trust.org/instruments/beck-depression-inventory-r-second-edition
Mental health	PHQ	A screening tool for mental disorders in primary care (various versions)	ePROVIDE: https://eprovide.mapi-trust.org/instruments/patient-health-questionnaire http://www.ncbi.nlm.nih.gov/pubmed/26268712
Pain	BPI	Widely used to assess the severity of pain and the impact of pain on daily functions	http://www.ncbi.nlm.nih.gov/pubmed/26268712 https://eprovide.mapi-trust.org/instruments/brief-pain-inventory
Pediatric			
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).	Child Outcomes Research Consortium: https://www.corc.uk.net/outcome-experience-measures/paediatric-quality-of-life-pedsql/
Pediatric HRQOL	PROMIS® Pediatric Instrument Banks	No information	National Institute of Arthritis and Musculoskeletal and Skin Disease: https://www.niams.nih.gov/grants-funding/niams-supported-research-programs/pediatric-patient-reported-outcomes-chronic

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; POLCA, Polycystic Liver Disease Complaint-specific Assessment; PRO, patient-reported outcome; PROM, patient-reported outcome measure; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; SF-12, 12-Item Short Form Survey version 2; SF-36, 36-Item Short Form Survey version 2; WHO, World Health Organization.

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 healthcare providers and patients being overwhelmed with too many and differing surveys.[898]

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).[899] Appendix Table 1 presents a summary of suggested PROMs appropriate for patients with ADPKD. Caveats about many of the PROMs are discussed in the Note column.

Additional PROMs

https://eprovide.mapi-trust.org/advanced-search

Implementation

Implementing PROMs in healthcare systems poses challenges. For a framework and examples see EIT Heath: https://eithealth.eu/wp-content/uploads/2020/05/Implementing-Value-Based-Healthcare-In-Europe_web-4.pdf

The International Society for Quality of Life Research SIG User's Guide to Implementing PROs Assessment in Clinical Practice: https://www.isoqol.org/wp-content/uploads/2019/09/2015UsersGuide-Version2.pdf

Appendix 2: Recommended checklist of issues to discuss at the beginning of the patient journey

Appendix Table 2| Discussion items for the beginning of the autosomal dominant polycystic kidney disease (ADPKD) patient journey

Discussion items	✓
The stages of PKD and what they may notice at each stage	
The range of trajectories for patients in terms of rate of progression	
The particular symptoms that they may develop (e.g., chronic pain, tiredness, bloating, swelling of abdomen) and the treatments they can request to deal with them	
The link to ADPLD	
The risk of passing on ADPKD to their children and testing of children	
Lifestyle changes they may need to adopt in order to mitigate the progression of ADPKD, such as diet, hydration, and exercise	
Support groups they can engage with	

ADPLD, autosomal dominant polycystic liver disease; PKD, polycystic kidney disease.

Appendix 3: Patient organizations dealing with ADPKD or kidney disease in general, and other useful resources for patients and healthcare providers

Patient organizations

Australia: PKD Australia: http://pkdaustralia.org
Belgium: AIRG Belgique: https://www.airg-belgique.org/fr/; https://www.airg-belgique.org/nl/
Canada: PKD Foundation of Canada: http://www.endpkd.ca
France: PKD France: http://www.polykystose.org [in French]
Germany: PKD Familiare Zystennieren e.V.: http://www.pkdcure.de [in German]
Italy: AIRP (Associazione Italiana Rene Policistico) ETS: http://www.renepolicistico.it [in Italian]
Japan: Polycystic Kidney Disease Foundation Chapter of Japan (PKDFCJ): http://www.pkdfcj.org [in Japanese]
Netherlands: nvn (nierpatienten vereniging nederland): http://www.nvn.nl/nierziekten-en-behandeling/nierziekten/cystenieren [in Dutch]
Spain: https://alcer.org/ [in Spanish]
Switzerland: SwissPKD: http://www.swisspkd.ch [in German]
UK: PKD Charity: http://www.pkdcharity.org.uk
USA: PKD Foundation: http://www.pkdcure.org

Resources from rare-disease organizations

Asia Pacific Alliance of Rare Disease Organisations: https://www.apardo.org/ [website]
Rare Voices Australia: https://rarevoices.org.au/ [website]
Kidney Health Australia: Polycystic kidney disease factsheet: https://kidney.org.au/resources/factsheets-and-photosheets/polycystic-kidney-disease-factsheet
European ADPKD Forum (EAF): The Brussels Declaration on ADPKD: https://pkdinternational.org/downloads/eaf-brusseles-declaration-2016/EAF_Brussels_Declaration_ENGLISH_March_2016.pdf
Association pour l'Information et la Recherche sur les maladies Rénales Génétiques (AIRG, France): La Polykystose Rénale Dominante Autosomique: https://www.airg-france.fr/wp-content/uploads/2017/05/pkd-edition-2017-num-3.pdf
National Organization for Rare Disorders (NORD, USA): https://rarediseases.org/rare-diseases/autosomal-dominant-polycystic-kidney-disease/ [website]
Orphanet (Europe): https://www.orpha.net/en/disease/detail/730 [website]
National Registry of Rare Kidney Diseases (RADAR, UK): https://ukkidney.org/rare-renal/patient/autosomal-dominant-polycystic-kidney-disease [website]