



PROPOSED SCOPE OF WORK FOR KDIGO CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION, MANAGEMENT, AND TREATMENT OF ADPKD

Scope of Work

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a major genetic disorder affecting up to 12 million individuals worldwide and the 4th most common global cause for kidney replacement therapy (KRT). A Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on ADPKD held in Edinburgh (January 16-19, 2014) brought together a panel of multidisciplinary experts and engaged patients from 20 countries. The panel assessed the state of knowledge and disparities among different countries and centers related to the evaluation, management, and treatment of ADPKD, identified outstanding knowledge gaps and controversial issues, and ascertained the timeline for the development of a clinical practice guideline made up of recommendations and practice points for ADPKD. Since then, large epidemiological studies and clinical trials have been completed and many others are ongoing; additional genes associated with ADPKD have been discovered; and the first pharmacologic treatment to slow disease progression has been approved by regulatory agencies. These advances 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 is most timely.

The framework for the planned KDIGO guideline for ADPKD has been adapted from the breakout topics of the KDIGO Controversies Conference. ADPKD is a chronic, progressive condition characterized by the development and growth of cysts in the kidneys and other organs and by additional systemic manifestations. It is genetically heterogeneous, most commonly caused by mutations to the *PKD1* or *PKD2* gene and rarely to other recently recognized genes. ADPKD is characterized by significant phenotypic variability, with most patients diagnosed after the third decade of life and

mild cases often going undiagnosed. Understanding the genetic and phenotypic complexity of ADPKD is critical for the diagnosis and prognosis of the disease ([Chapter 1](#)). The kidney manifestations of the disease (e.g., hypertension, kidney stones, cyst hemorrhage or infection, and kidney pain) occur commonly early in the course of disease and often lead to the diagnosis ([Chapter 2](#)). The most frequent and clinically significant complications in the majority of patients with ADPKD are hypertension, the development of CKD, and kidney failure. There is increasing evidence that early conservative management including dietary interventions, hydration, and rigorous blood pressure control can have a substantial impact on the long-term outcome of the disease. Some aspects of kidney replacement therapy are also specific to patients with ADPKD ([Chapter 3](#)).

Until very recently, there had not been disease-modifying therapies available and the treatment of ADPKD has been limited to management of its complications. Beyond conservative management, some treatments targeting cyclic AMP signaling have shown to be effective. One agent, tolvaptan, slows the growth of the kidneys and the decline of kidney function. Somatostatin analogues slow the growth of the kidneys and liver, but no consistent effect on the decline of kidney function has been demonstrated. Many clinical trials are now in progress, while non-pharmacological interventions are being utilized ([Chapter 4](#)).

ADPKD is a systemic disorder and polycystic liver disease is often a manifestation of ADPKD which can occur as a genetically distinct entity, in the absence of or with only few kidney cysts. When severe (as more commonly in women), it may require treatment which importantly needs to be individualized ([Chapter 5](#)). In addition to the liver, ADPKD can affect other organs or tissues. One case in point is intracranial aneurysm, which is most important because of the high morbidity and mortality associated with aneurysmal rupture. There are also other extrarenal manifestations that affect the heart, skeletal muscle, gastrointestinal tract, pancreas, meninges (arachnoid and dura), lung, spleen, and testes ([Chapter 6](#)).

Beyond the kidney and extrarenal manifestations of the disease, ADPKD also impacts affected individuals in psychological and socioeconomic terms. Anxiety and depression are highly prevalent. Issues related to coping with the diagnosis such as effects on lifestyle, reduced life expectancy, reproductive choices; associated feeling of guilt, body image, chronic pain; need for kidney replacement therapy; impact on career and financial means should be recognized and addressed ([Chapter 7](#)). Patients with ADPKD should be informed about reproductive choices, including whenever feasible preimplantation genetic diagnosis, and risks of pregnancy which depend on the severity of CKD ([Chapter 8](#)).

Much less is known about the manifestations and progression of ADPKD in children compared to adults. This is particularly striking because early interventions are likely to be most effective to treat the disease. Furthermore, diagnostic and treatment protocols for childhood ADPKD may vary widely from country to country and among centers. Issues specific to childhood ADPKD will be embedded into a chapter dedicated solely to childhood ADPKD (Chapter 9).

The optimal model of care for a complex, inherited, systemic disorder such as ADPKD likewise requires specific, multi-level expertise to ensure that patients and their family have access to appropriate clinical experts and current standards of care and support while working collaboratively with patient organizations to foster research and advance the understanding and treatment of ADPKD and improve outcomes for the affected patients (Chapter 10).

CHAPTER OUTLINE AND CLINICAL QUESTIONS

Chapter 1. Diagnosis and prognosis

- What is ADPKD?
 - Clinical definition
 - Imaging definition – cyst number criteria
 - Genetic definition – should genes other than *PKD1* and *PKD2* be considered ADPKD?
 - Consideration of family history
- What is ADPLD? (overlap with Chapter 5)
 - Clinical definition
 - Imaging definition – cyst number criteria
 - Genetic definition – what genes to include
 - Consideration of family history
- How do we differentially diagnose ADPKD from related disorders?
 - Genetic screening - what type of analysis should be performed?
 - Imaging?
 - Clinical phenotype
 - Disorders to consider:
 - ARPKD, syndromic ciliopathies, autosomal dominant tubulointerstitial kidney disease (ADTKD), TSC, TSC-PKD1-CGS, HNF1B, ADPLD, OFD1, COL4A3/4/5, other
- How do we define other monoallelic causes of kidney cysts?
 - *GANAB*, *DNAJB11*, *ALG9*
- What naming scheme should we use for ADPKD and related diseases?
 - Should the disease and gene name be included?
 - Should allelic information be included?
- What analysis is appropriate for older subjects with bilateral cysts, sometimes mild CKD, and no clear family history of PKD?
 - Genetic screening – what type of analysis should be performed?
 - Imaging – sensitive analysis
 - Clinical evaluation
 - Family screening of adult relatives?
- Can we clinically exclude ADPKD as a diagnosis? If yes, how and at what age?
- How and when should asymptomatic adults at risk of ADPKD be screened?
 - Genetic screening – what type of analysis should be performed?
 - Imaging
 - Clinical evaluation – blood pressure (BP), etc.
 - Educational materials and counseling

- Psychological and social issues about being (or not) tested/diagnosed, early psychosocial aspects directly after diagnosis
- How and when should symptomatic adults with ADPKD undergo genetic testing?
- How and when should asymptomatic children at risk of ADPKD be screened? (overlap with Chapter 9)
 - Genetic screening – what type of analysis should be performed?
 - Imaging – which modality (ultrasound, MRI, other)?
 - Clinical evaluation – BP etc. – is hypertension in a child at risk sufficient to establish the diagnosis? Which modality to assess BP in this population?
 - Educational materials and counseling
 - Psychological and social issues about being (or not) tested/diagnosed, early psychosocial aspects directly after diagnosis
- What is the role for preimplantation genetic diagnosis in ADPKD? (overlap with Chapter 8)
- How can we predict the severity of kidney disease in ADPKD in adults? (overlap with Chapters 3 & 4)
 - Imaging analysis - Mayo Imaging Class
 - Genetic analysis – genic and allelic data
 - Clinical information
 - Family history?
 - Urine biomarkers?
 - Combined analysis of factors – PROPKD score
 - Based on this data, who should we consider as a rapidly progressing patient?
- How can we predict the severity of kidney disease in ADPKD children? (overlap with Chapter 9)
 - Imaging analysis
 - Genetic analysis – genic and allelic data, biallelic, digenic disease
 - Clinical information – BP, proteinuria
 - Family history?
 - Urine biomarkers?
 - Combined analysis of factors
 - Based on this data, can we predict rapidly progressing patients?
- What is the natural history of:
 - *PKD1-T*, *PKD1-NT* & *PKD2* associated ADPKD?
 - *PKD1* mosaicism?
 - *GANAB*, *DNAJB11*, *ALG9* associated nephropathy?
- How should we define childhood ADPKD? (overlap with Chapter 9)
 - What is the definition of early onset (EO) and very early onset (VEO) ADPKD?

- Role of genetics, biallelic and complex genotypes
- Role of imaging
- Is there a role for population screening to detect affected individuals?

Chapter 2. Kidney manifestations

2.1: Hypertension

- What is the pathogenesis of hypertension in ADPKD?
- What is the optimal BP target in adults with ADPKD?
- What is the role of home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM) in adults with ADPKD?
- What is the role of non-pharmacologic interventions for BP control in adults with ADPKD?
- Which are the preferred antihypertensive agents in adults with ADPKD?
- When would it be appropriate to suspect other secondary causes of hypertension in adults with ADPKD?
- How should hypertension related end organ damage be evaluated in ADPKD?

2.2: Nephrolithiasis

- When and how should patients with ADPKD be screened for kidney stones?
- When and how should patients with ADPKD be counselled on measures to prevent kidney stones?
- When should patients with ADPKD and kidney stones undergo metabolic evaluation to identify factors contributing to stone formation?
- What are benefits and harms of treatments for stones in ADPKD?
- What follow-up is recommended for patients with ADPKD and stone disease?
- How is the medical or surgical treatment of nephrolithiasis in ADPKD different from that of nephrolithiasis in patients without ADPKD?

2.3: Urinary tract and kidney cyst infections

- When and how should patients with ADPKD be counselled on measures to prevent urinary tract infections (UTI)?
- When should asymptomatic pyuria/bacteriuria be investigated in patients with ADPKD?
- When should patients with ADPKD undergoing urologic procedures or bladder catheterizations receive prophylactic antibiotics?
- What are the differences in the evaluation and treatment of an infection of the low urinary tract in patients with ADPKD compared to patients without ADPKD?
- What are the differences in the diagnosis, evaluation, and treatment of acute pyelonephritis in patients with ADPKD compared to patients without ADPKD?

- When is it appropriate to suspect a kidney cyst infection in patients with ADPKD and how should the infection be diagnosed?
- How to differentiate between liver and kidney cyst infections?
- How and for how long should a kidney cyst infection be treated?
- When is it appropriate to suspect unusual kidney infections in ADPKD (e.g., emphysematous pyelonephritis, fungal, mycobacterial)?
- What are the benefits and harms of prophylactic treatments?

2.4: Kidney cyst hemorrhage and/or hematuria

- What recommendations should patients with ADPKD receive to reduce the risk for cyst hemorrhage and/or gross hematuria?
- When is it appropriate to suspect an acute cyst hemorrhage, subcapsular hemorrhage, or retroperitoneal hemorrhage in ADPKD? How should it be diagnosed and treated?
- What are measures to evaluate and treat episodes of gross hematuria in ADPKD?
- What are measures to evaluate microscopic hematuria in patients with ADPKD?

2.5: Renal cell carcinoma (RCC)

- Is there an increased risk of RCC in patients with ADPKD, compared to the general population or patients with other kidney diseases?
- What are the benefits of screening adults with ADPKD for RCC? What age is appropriate for screening? How often should adults with ADPKD be screened?
- What clinical presentations should raise concern for the presence of RCC in adults with ADPKD?
- What imaging findings should raise concern for the presence of RCC in adults with ADPKD?
- What are the differences in the treatment of RCC in the setting of ADPKD compared to patients without ADPKD?
- Do monitoring guidelines change in patients with contiguous gene syndrome due to risk of RCC?

2.6: Chronic kidney pain

- How should chronic pain be defined versus acute kidney pain caused by infection, stones, or bleeding? What causes chronic kidney pain in ADPKD?
- How good is the relationship between chronic pain and kidney volume?
- What tests should be used to evaluate adults with ADPKD and chronic kidney pain?

- What other specialists should be included in the multidisciplinary team to evaluate and treat adults with ADPKD and chronic pain?
- What is the role of non-pharmacological, non-invasive interventions (e.g., physical therapy, complementary medicine, transcutaneous electrical nerve stimulation (TENS), cannabidiol (CBD), etc.) to treat patients with ADPKD and chronic pain?
- When and how should a stepwise pharmacological treatment be implemented in patients with ADPKD and chronic pain?
- When should the following be considered in patients with ADPKD and chronic pain:
 - Diagnostic cyst aspiration or therapeutic sclerotherapy?
 - Laparoscopic fenestration?
 - Nerve blocks or kidney denervation?
 - Spinal cord stimulation?
 - Nephrectomy (preferably laparoscopic)?
- What is the best management approach for adult patients with ADPKD, chronic kidney pain, and opiate addiction?

2.7. Gout

- What are the risk factors for the development of gout in ADPKD (e.g., reduced blood flow, diuretics, others)?
- Should a diagnosis of ADTKD be considered in patients with cystic but not enlarged kidneys?
- Is the treatment of gout in ADPKD different from that in patients without ADPKD?

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

3.1. CKD progression

- What are the known genetic and non-genetic risk factors for ADPKD progression?
- What biomarkers predict ADPKD progression?
- What is the relationship between rates of kidney growth and glomerular filtration rate (GFR) decline in ADPKD?
- What rates of kidney growth and GFR decline are used to define the severity of the disease?
- How often and how should the structural and functional progression of ADPKD and CKD be monitored in adults with ADPKD? How often should we perform MRI?
- What factors other than cystic expansion contribute to the decline of GFR in ADPKD?

- How should cardiovascular risk factors and cardiovascular health be monitored and treated?
- How should diet and medications be adjusted as the disease progresses?
- What factors should be considered in the choice of kidney replacement therapy?
- Can CKD personalized risk tools be used on ADPKD to predict kidney replacement therapy or is there a need for a new ADPKD risk tool?

3.2: Kidney transplantation:

- When should patients be referred to the transplant clinic? Are there differences between ADPKD patients and other CKD patients?
- What guidelines are appropriate to rule out ADPKD in living, related potential kidney donors?
- In addition to tests for all patients being evaluated for kidney transplantation, what additional testing is required for the patients with kidney failure due to ADPKD?
- What are the indications for removing the native polycystic kidneys? What are objective size criteria to determine when an ipsilateral, noninfected native kidney must be removed solely based on volume? If indicated, when is the best time and surgical approach for the nephrectomy(ies)?
- What are the factors to consider when selecting a particular immunosuppressive regimen because of the diagnosis of ADPKD or polycystic liver disease (PLD)?
- Should preemptive living donor transplantation always be prioritized?
- Are patients with ADPKD compared to non-ADPKD CKD patients at increased risk for specific complications after kidney transplantation (e.g., cyst infections, cardiovascular events, skin cancers, bone fractures, etc.)?
- Are the approaches to kidney transplant and the treatment post-transplant different for contiguous gene syndrome PKD1/TSC2?

3.3: Chronic dialysis:

- When should dialysis education be initiated, vascular access be created, or peritoneal dialysis catheter inserted?
- When is chronic dialysis or peritoneal dialysis rather than kidney transplantation necessary or indicated?
- What factors favor hemodialysis or peritoneal dialysis in ADPKD patients?
- What are the contraindications of ADPKD patients to peritoneal dialysis?
- Are patients with ADPKD on hemodialysis or peritoneal dialysis at increased risk for disease specific complications?
- How should chronic ADPKD dialysis patients be monitored for RCC (see point 2.5)?

- What are the indications for native nephrectomy in a dialysis patient who is not an immediate transplant candidate? (overlap with Section 3.2)
- How should anticoagulation, antiplatelet therapy be managed in an ADPKD patient on dialysis?
- What is the appropriate blood pressure control for ADPKD patients on dialysis?
- What special considerations should be given to treatment of patients with known brain aneurysm on dialysis? What is the preferred dialysis modality? How should BP be managed?
- How to manage pericardial effusions found in ADPKD? Are they exacerbated on dialysis? What is the effect of uremia?

Chapter 4. Nonpharmacologic and pharmacologic therapies to delay ADPKD progression

- In addition to blood pressure control (see above), which of the following nonpharmacologic treatments should be considered to slow the progression of ADPKD:
 - Dietary sodium restriction?
 - Dietary protein restriction?
 - Caloric restriction to maintain optimal body mass index (BMI)?
 - High water intake to suppress vasopressin release?
 - Dietary phosphate restriction?
 - Dietary acid restriction or bicarbonate supplementation?
 - Restriction in caffeine (or other xanthins, their) intake?
- When should these restrictions be started? How long should they last?
- What biomarkers (if any) be used to screen for excess dietary sodium intake and/or monitor progress of nonpharmacologic treatments (such as spot or 24-hour urine sodium, serum copeptin)?
- When is referral to a dietitian indicated?
- What is the role of special diets (Mediterranean, DASH, vegetarian, low osmolar, ketogenic, intermittent fasting) in patients with ADPKD?
- How much water intake is appropriate for a person with ADPKD? Should it be higher compared to someone without ADPKD?
- What is the optimal weight/BMI for a person with ADPKD?
- Who should be considered for a pharmacologic treatment potentially delaying kidney disease progression in ADPKD?
- Which specific subgroups of ADPKD patients are more prone to benefit from these treatments? What are the criteria?
- How do we define rapid progressors in ADPKD: by estimated GFR slope?, family history?, Total kidney volume (TKV) – Mayo Score, PROPKD score?, other? (overlap with Chapter 1)

- What are the respective roles, if any, for these potential treatments in patients with ADPKD:
 - mTOR inhibitors?
 - Vasopressin V2 receptor antagonists (tolvaptan, lixivaptan)?
 - Somatostatin analogues (octreotide, lanreotide, pasireotide)?
 - Tyrosine kinase inhibitors (tasevatinib)?
 - Glucosylceramide synthase inhibitor (venglustat)?
 - Nrf2 activators (bardoxolone)?
 - Statins?
 - Metformin or other AMPK activators?
 - Niacinamide?
 - Others (e.g., pioglitazone, hydralazine)?, Stem-cell based therapies?, 2-deoxy-glucose?
- How should treatment efficacy be monitored?
- What ADPKD patients are more likely to be informative in clinical trials?
- Should patients with the contiguous gene syndrome PKD1/TSC2 and angiomyolipoma (AML) >3 cm be treated with mTOR inhibitors?
- What is the role of real-world evidence (RWE, based on registries, databases, electronic medical records) in clinical trials on ADPKD?

Chapter 5: Polycystic liver disease (PLD)

- Who should be screened for PLD?
- Which modality should be used to diagnose PLD?
- How do we define the magnitude of PLD? Place of total liver volume (TLV) versus other classifications? Like TKV, should TLV be related to height?
- What dietary measures should be applied by people with PLD?
- What lifestyle adjustments should be made by people with PLD?
- What are the specific recommendations about use of estrogen (or exogenous hormones) in women with cysts in the liver? What is the risk of multiple pregnancies to women with cysts in the liver?
- Is there a different risk for estrogen- versus progesterone-containing contraceptives?
- Is menopausal hormone therapy contraindicated in PLD? What is the risk of vaginal estrogens?
- What are the indications to treat PLD: criteria?, quality of life?
- What is the best approach for treating PLD? Which modality, duration, follow-up?
- What is the appropriate medical treatment for PLD? Somatostatin analogues?, ursodeoxycholic acid?, mTOR inhibitors?, others?
- What is the appropriate percutaneous therapy for PLD? Cyst aspiration and sclerosis?, embolization?, other?

- What is the appropriate surgical therapy for PLD? Fenestration?, liver resection?, liver transplantation?
- What is the appropriate diagnosis (labs, imaging, PET) and management (choice of antibiotics, duration of treatment) of liver cyst infection? Is there a place for percutaneous cyst drainage?
- How should one grade and stage PLD?
- How should the threshold for live transplantation be defined?
- What is the role of (selective decontamination of the digestive tract [SDD] or non-SDD) prophylaxis on the recurrence of cyst infection?
- What is the natural course of PLD? Is there variability among patients?
- Is the value in using a disease-specific questionnaire for PLD? How should these be used? When does it help to steer management?

Chapter 6. Intracranial aneurysms (ICA) and other extrarenal manifestations

6.1: Intracranial aneurysms (ICA):

- What are the risk factors for the development or rupture of ICA in the general population and in patients with ADPKD? Is there a role for blood pressure control, which level? Are specific headache complaints predictive?
- What are the general recommendations to prevent the development or rupture of ICA by targeting modifiable risk factors?
- Is presymptomatic screening for ICA indicated in patients with ADPKD or ADPLD?
- If so, what is the rationale favoring universal or targeted screening?
- If presymptomatic screening is indicated, at which age should screening be started? If the presymptomatic screening for ICA is negative, how often to re-screen? And in the case repeated screening is indicated, until which age should it be continued? Should presymptomatic screening be considered prior to major elective surgery (e.g., kidney transplantation) and/or pregnancy?
- What is the most appropriate diagnostic test to screen for ICA in ADPKD? How should this be tailored to level of kidney function?
- How should ICA detected by presymptomatic screening be managed? When should the patient be referred to a cerebrovascular neurologist, interventional radiologist, neurosurgeon?
- Is there an increased risk of complications of neurosurgical or endovascular intervention in ADPKD patients compared to the non-ADPKD population?
- Are the long-term outcomes of those who have suffered a subarachnoid hemorrhage different to those in the general population?

6.2: Other vascular associations:

- When and how should a patient with ADPKD be screened for aortic root dilation, thoracic aortic aneurysms, and dissections? Which modality?
- Are ADPKD patients at increased risk for carotid, vertebral, or coronary artery dissections?

6.3: Cardiac associations (e.g., left ventricular hypertrophy, valvular heart disease, atrial fibrillation, idiopathic cardiomyopathies, and congenital heart disease)

- What is the best approach to screening for cardiac associations in ADPKD?
- What symptoms or clinical findings should trigger echocardiography and/or cardiology consultation be requested for people with ADPKD?

6.4: Muscle-skeletal manifestations

- Are abdominal wall hernias more common and clinically significant in patients with ADPKD?
- Is the treatment of hernias different in ADPKD compared to the general population?
- Do adult patients with ADPKD have an increased risk for osteopenia/osteoporosis and/or bone fractures and/or skeletal malformations?

6.5: Other associated cysts and diverticula

- What is the clinical significance of the following in ADPKD and are specific recommendations or further evaluation indicated:
 - Dilated extrahepatic bile ducts?
 - Pancreatic cysts and/or intraductal papillary mucinous neoplasms (IPMNs)?
 - Arachnoid cysts?
 - Dural diverticula?
 - Seminal vesicle, epididymal, prostate, testicular cysts?
 - Ovarian cysts?
 - Colonic diverticula?
 - Duodenal or small bowel diverticula?
 - Bronchiectasis and pulmonary cysts?

Chapter 7. Lifestyle and psychosocial aspects

- What type of physical activity is inappropriate or not advisable for patients with ADPKD? Are there risk factors for such restrictions (e.g., contact sports)? Which children/patients with ADPKD should be restricted from contact sports?
- What advice should be given to persons with ADPKD in terms of smoking cessation?

- Which lifestyle recommendations should be provided to a person with ADPKD?
- When and how should persons with ADPKD be screened for anxiety and depression?
- Which psychosocial issues should be reviewed in persons with ADPKD?
- Which psychosocial support should be provided to persons with ADPKD:
 - Pain management?
 - Self-management?
 - Social challenges?
 - Psychological issues?
 - Education and information about genetics?
 - Treatment modalities in general, clinical trials, self-monitoring (e.g., blood pressure control), etc.?
 - Referral to peer support (hospital based or provided by patient group)?
- Is life expectancy lower in ADPKD?
- What is the impact of ADPKD on body image or sexual dysfunction?
- What are the financial impacts of ADPKD (career, income, insurance)?
- What is the psychosocial impact of screening ADPKD in childhood?
- What is the impact of “guilt feeling” (e.g., dominant mode of transmission) on transmission of the disease?
- Who should inform the offspring on the risk of having ADPKD? At what age should they be screened? What is the role of the child/teen in electing to undergo screening?
- What is the psychosocial impact on family planning?
- Who can elect screening (child vs. parent)? How should this screening be performed?

Chapter 8. Pregnancy, reproductive issues and choices

8.1: Pregnancy

8.1.1: Mother

- What are the specific risks for pregnancy in ADPKD women? What is the impact of CKD stage? Are there special considerations?
- Do pregnancies impact long-term outcomes of ADPKD regarding kidney function and hypertension? Is the number of pregnancies a factor?
- Has pregnancy any impact on liver disease in ADPKD (repeated pregnancies, repeated hormonal stimuli)?
- Is there harm associated with multiple pregnancies in some women with ADPKD?
- How should pregnant women with ADPKD be monitored? Are there specific measures for maternal follow-up during pregnancy in ADPKD?

- What are the specific blood pressure targets for pregnant women with ADPKD? Which antihypertensive agents should/should not be used both in pregnancy and breast-feeding?
- How are UTIs, and kidney and liver cyst infections prevented and managed in pregnant women with ADPKD?
- How are acute or chronic abdominal/lumbar pain managed in pregnant women with ADPKD?
- Is there an increased risk for ICA rupture during pregnancy in women with ADPKD?
- Are there special delivery procedures for women with ADPKD? What is the influence of TKV–TLV?
- Are there specific measures for post-partum care and follow-up in women with ADPKD?
- What recommendations are there for ADPKD women post-transplant and pregnancy?

8.1.2: Fetus

- When should prenatal sonography be performed in women with ADPKD or with a partner with ADPKD? Which modalities should be used for sonography in pregnant women with ADPKD? What specific features should be searched for?
- Which specialties should be involved in counseling a prenatal form (geneticist, pediatric nephrologist, adult nephrologist, neonatologist)?
- What are the issues regarding the diagnosis/prognosis/termination of pregnancy (TOP) indication in counseling a prenatal case with nephromegaly and/or hyperechogenic kidneys and/or kidney cysts and/or oligohydramnios when ADPKD is suspected?
- What implications do first diagnosis in ADPKD in a fetus have for the parents and the family?

8.2: Reproductive issues

- How should preconception counseling be performed? What type of reproductive counseling should patients at risk of ADPKD receive? Who should be involved?
- What is the preferred contraception method in ADPKD? Estrogen-free birth control pill? Is there evidence in teens/young women? Are intrauterine devices contraindicated?
- What are the benefits of screening male subject with ADPKD for reproductive system abnormalities?

8.2.1: Options to prevent the birth of an affected child

- What is the role of pre-implantation genetic testing (PGT) to patients with ADPKD? (refer to Chapter 1)
- Which technique should be used for PGT? Is there any specific risk associated with methods used for ovarian stimulation?
- Is there restriction for in vitro fertilization (IVF) generally (e.g., for patients with cystic liver)?
- Are there particular risks for IVF pregnancies in ADPKD?
- What are the chances of a successful pregnancy using PGT?
- Is PGT available in all countries? Should ADPKD be among the reimbursed PGT cases in all countries?
- What is the role of prenatal diagnosis to patients with ADPKD?
- What is the role of sperm donation or ovidonation to patients with ADPKD?

Chapter 9. Pediatric issues

- How do we diagnose ADPKD in children?
 - Which features support the prenatal diagnosis?
 - What are the imaging criteria which define diagnosis?
 - Are there clinical criteria in at-risk children that would already define diagnosis without imaging? How do we call hypertension and proteinuria in an at-risk child without previous imaging?
 - What is the role of different imaging modalities in the diagnosis of pediatric ADPKD (US/3DUS/MRI/CT)?
 - How would we differentiate ADPKD from other cystic kidney diseases in children? Clinical criteria? Imaging (abdominal ultrasound)?
 - What is the definition of VEO and EO ADPKD?
 - What are the diagnostic features of contiguous gene syndrome PKD1/TSC2?
 - What is the role of genetic testing for diagnosis of pediatric ADPKD?
 - Which genes should be screened? Which clinical/imaging/family history features suggest that an expanded genetic panel (e.g., ciliopathies) is indicated?)
 - How does a negative family history impact the diagnostic criteria?
 - Are there specific considerations for diagnosis in the setting of:
 - Prenatal screening?
 - Incidental finding?
 - Symptomatic (e.g., hematuria, UTI, etc.) screening?
 - Asymptomatic screening because of the context of familial history?
- What are the clinical manifestations in children with ADPKD?

- Hypertension
 - What level of BP (P75-P95->P95) requires treatment and what is the optimal BP target (P75-P50) in children with ADPKD?
 - What is the role of non-pharmacologic interventions for BP control in children with ADPKD? What is the role of instituting health habits with respect to exercise and diet (sodium) early in life in at-risk or ADPKD children, even prior to detection of elevated BP? Targeting normal BMI?
 - What is the role of HBPM and ABPM in diagnosis/management of children with or at-risk for ADPKD?
 - Which are the preferred antihypertensive agents in children with ADPKD?
 - When would it be appropriate to suspect other secondary causes of hypertension in children with ADPKD?
 - When would we screen for complications (cardiac evaluation, left ventricular mass index (LVMI), hypertensive retinopathy, and proteinuria)?
 - Do recommendations differ from hypertension in the general pediatric population?
 - Should nocturnal hypertension be treated in ADPKD children? To what goal?
 - What would be adequate next steps in an at-risk child without previous imaging with hypertension on ABPM? Imaging or not?
- UTIs and dysfunctional voiding
 - How should UTI be managed in children with ADPKD?
 - How should we manage enuresis in children with ADPKD?
 - When is it appropriate to suspect a kidney cyst infection in patients with ADPKD and how should the infection be diagnosed?
- Other kidney manifestations
 - What are the special considerations in affected children with nephrolithiasis? Is it worth to screen for hypocitraturia?
 - What are the special considerations in children with ADPKD and cyst hemorrhage and/or hematuria?
 - What is the definition of proteinuria/microalbuminuria in ADPKD children?
 - Do monitoring guidelines change in children with contiguous gene syndrome due to risk of RCC?
 - What are the special considerations in children affected with ADPKD and acute/chronic pain?
- Extrarenal manifestations
 - What is the frequency of the following abnormalities in children with ADPKD:
 - Liver?

- Pancreas cysts?
 - Intracranial aneurysm?
 - Hernia?
 - Cardiac valve abnormalities?
 - Should we screen children with ADPKD for extrarenal manifestations? At what age and how often?
- What is the prognosis of ADPKD children?
 - How should ADPKD severity be determined in children?
 - What is the role of age of symptomatic presentation (VEO/EO) in the prognosis?
 - Family history phenotype (age of KRT)?
 - Genetic analysis – genic and allelic data, biallelic, digenic disease?
 - Clinical information – hypertension, proteinuria, UTI?
 - Urine biomarkers?
 - How should ADPKD progression be monitored in children?
 - What is the outcome of VEO/EO children with ADPKD?
 - What is the role of imaging in defining progression in children with ADPKD?
 - What are the structural kidney disease markers which are most reflective of disease progression in ADPKD children (e.g., TKV, height-adjusted TKV, body surface area (BSA)/BMI-adjusted TKV, cystic volume and cyst numbers?
 - What is the correlation of cyst volume to TKV?
 - How do we differentiate the normal kidney growth from PKD progression?
 - What is the value of kidney function in defining progression in children with ADPKD?
 - How common is glomerular hyperfiltration in pediatric ADPKD? How is it defined and what is the clinical significance with respect to progression/long-term risk?
 - What is the best method to calculate eGFR in children affected with ADPKD? What is the role of cystatin C?
 - What is the incidence of CKD in children affected with ADPKD?
- What are the special considerations in the treatment of children with ADPKD?
 - How do we evaluate and follow neonates with prenatal ADPKD diagnosis?
 - Is there evidence to support high water intake in childhood ADPKD? What are the age-specific risks of this intervention?
 - Which dietary interventions are appropriate for children with or at-risk of ADPKD? What are the risks for protein/calorie restriction in childhood?

- What are the potential targeted treatments? Statin?, tolvaptan?, metformin?, curcumin?
 - Who should be considered for treatment? VEO? What are the particular risks of interventions in VEO and pediatrics due to age/size of child?
 - When should we start treatment for proteinuria/hypertension?
 - Which drugs should be used for the treatment for proteinuria/hypertension?
 - Should non-pharmacological treatments be considered in children with ADPKD and at-risk for ADPKD?
 - What is the benefit of sports/exercise participation in the management of children with or at-risk for ADPKD? What are the risks of contact sports in children with ADPKD regarding cyst trauma?
 - Should ADPKD children specifically be advised to avoid smoking?
 - What is the value of developmentally appropriate educational material to support the management of children with ADPKD?
 - What is the value of educational materials to specifically support parents when they have a child with ADPKD or at-risk for ADPKD?
- What are the considerations for screening of at at-risk children in the context of familial ADPKD?
 - How should we screen asymptomatic at-risk children for ADPKD (genetic/imaging/clinical evaluation)?
 - What are the potential pitfalls of radiographic screening to exclude ADPKD in at-risk children? If radiographic screening is negative, how often should it be repeated if the family desires ongoing screening?
 - What are the issues regarding elective genetic screening for at-risk asymptomatic children with respect to future insurability life/disability?
 - At what age should children at-risk of ADPKD be screened for hypertension and how (HBPM/ABPM?)? How frequently should screening be repeated?
 - Which steps should be taken after identifying a child at-risk of ADPKD with hypertension?
 - At what age should children at-risk of ADPKD be screened for proteinuria and how? How frequently should screening be repeated?
 - Who should be involved in the decision-making for screening (e.g., parents, child, general practitioner, pediatrician, nephrologist, geneticist)?
 - Psychological and social issues about being/not being tested/diagnosed, early psychosocial aspects directly after diagnosis (Chapter 7)

- Are there specific issues to take into account for the transition of children with ADPKD to adult nephrology care?

Chapter 10. Approaches to management of patients with ADPKD

- What is the evidence from other chronic conditions or rare diseases for the benefit from multidisciplinary care (e.g., cystic fibrosis, diabetes, “highly specialized commissioned services’ in the United Kingdom)?
- What models of shared care would work in ADPKD?
- What models of self-management would work in ADPKD, including nutritional advice, BP monitoring, etc.?
- What evidence is there that shared decision-making improves outcomes in ADPKD?
- What models of telemedicine can be utilized to facilitate management of patients who live remotely from a reference center (e.g., for routine clinics)?
- What constitutes an ideal lifelong patient management pathway or journey in ADPKD (e.g., European ADPKD Forum (EAF) route map)?
- What should constitute an optimal multidisciplinary clinic for ADPKD?
- Is there a health economics benefit to the national health services and patients?
- What models of transition would work in ADPKD?
- What lessons can be learned from the management of other rare diseases which could apply to ADPKD (e.g., European Reference Networks)?
- What is the place of patient organizations to the model of care for ADPKD (adults and pediatrics)?
- Should ADPKD be considered as a “rare disease”?