FRAMEWORKS
in Health and Quality

Collaborating for Improved ADPKD Management

Considerations for the Healthcare Team

A Resource for Providers

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Considerations for the Healthcare Team

Although it is a rare disease, **ADPKD is the fourth leading cause of kidney failure**.[1]

What is PKD?

Polycystic kidney disease (PKD) is the most common genetic cause of end-stage renal disease.[2]

PKD is broadly divided into three types[2,3]:

- Autosomal recessive polycystic kidney disease (ARPKD)
- Autosomal dominant polycystic kidney disease (ADPKD)
- Syndromic disorders

What is ADPKD?

Most cases of ADPKD are caused by the PKD mutation's more severe phenotype.[4,5]

PKD1* mutations | 85%[4,5]

- Cysts may appear when patients are young adults or even earlier, and the disease can progress rapidly.[6]
- Average age of end-stage renal disease (ESRD) onset is roughly 54 years.[5]

PKD2† mutations | 15%[4,5]

- The disease progresses more slowly.[5]
- Average age of ESRD onset is roughly 74 years.[5]

*PKD1=gene that encodes polycystin 1 (PC1), a transmembrane protein located on the cilia and epithelial cells of the renal tubules.[5,7]

†PKD2=gene that encodes polycystin 2 (PC2), a nonselective cation channel located on the cilia and endoplasmic reticulum of the renal tubule epithelium.[5,7]

Prevalence of ADPKD

- ADPKD is a rare disease.[8]
- Estimated prevalence of **~140,000 diagnosed cases** in the United States in 2017[9]
  - Consistent with prevalence estimates worldwide

European Union | 3.3:10,000[10] **Japan** | 1.4,033[11]

ADPKD is an autosomal dominant disease[5]

- Each child of a person with ADPKD has a **50% chance of inheriting the abnormal gene**.[5]
- **While ADPKD is an inherited condition, the age of onset and rate of progression can be unpredictable**, varying from patient to patient, even in the same family.[4]

ADPKD is a progressive kidney disease[2,5]

ADPKD is characterized primarily by the development and progressive enlargement of fluid-filled renal cysts.[2,5]

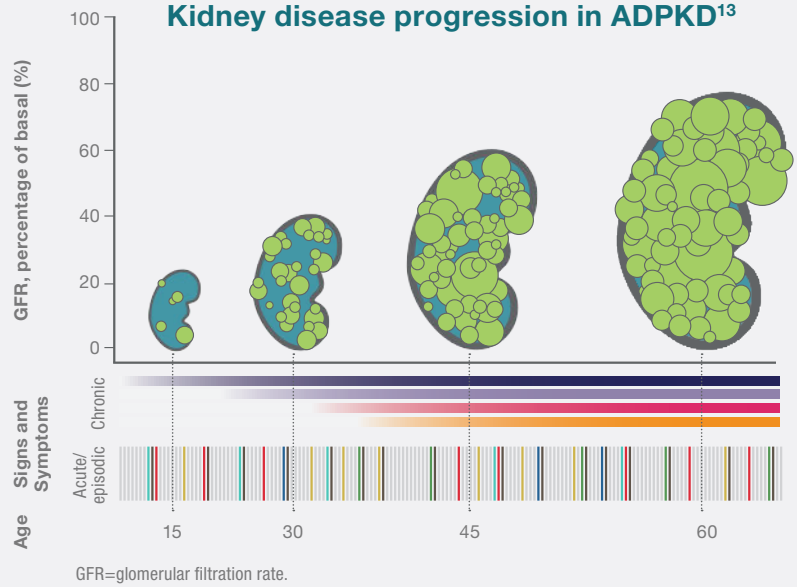
Kidney size ranges from minimally or moderately enlarged in early disease to **more than 20 times the normal size** in advanced disease. This contributes to compression and loss of the surrounding functional renal tissue, resulting in a progressive decline of renal function.[2,3,5]

More than 50%

of patients with ADPKD

will reach ESRD by age 60.[12]

Kidney disease progression in ADPKD[13]



GFR=glomerular filtration rate.

Chronic
- Urinary concentrating defects
- Hypertension
- Dull pain and discomfort
- Proteinuria

Acute/episodic
- Cyst rupture
- Hematuria
- Cyst infection
- Kidney stones
- Urinary tract infection
- Pain

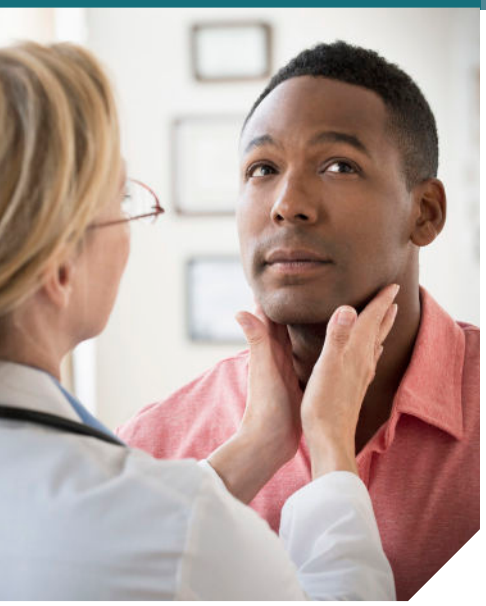
ADPKD can progress at different rates[5]

Depending on the type of mutation and other risk factors at the root of ADPKD[5]:

- Some patients may develop detectable cysts at 20 years of age.[5]
  - Rapidly progress to ESRD by age 50 years
- Other patients may have ADPKD that progresses more slowly.[5]
  - May not reach ESRD until they are 70 years old

Patients who have a family history of ADPKD or ESRD can undergo imaging and genetic testing to confirm whether they have the disease.[14]

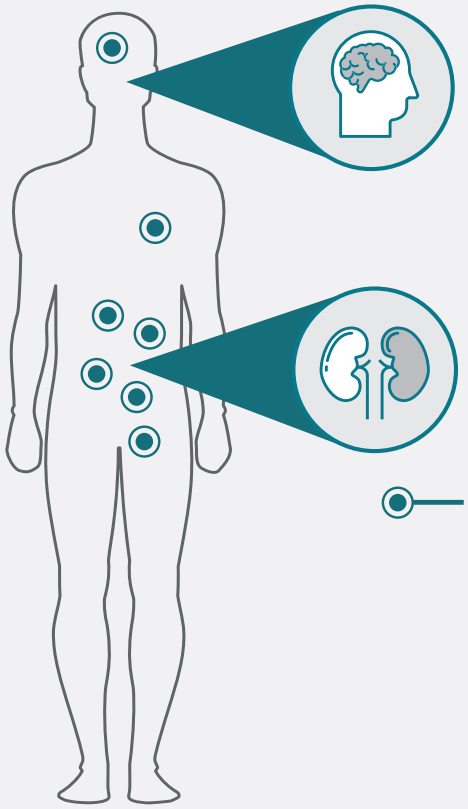
Considerations for the Healthcare Team



ADPKD often presents as nonspecific symptoms, so many people may actually live with ADPKD for years before this kidney condition is recognized[15]

- Even though ADPKD is a hereditary disease, family history may be unknown, and patients may not see a link between symptoms and the disease.[15]
- Initial signs or symptoms associated with ADPKD can include[3,15]:
  - Hypertension
  - Flank pain
  - Hematuria and proteinuria
  - Urinary tract infection (UTI)
- Early occurrence of these symptoms can be the most important predictive indicators of rapid progression.[3,15]

ADPKD is a systemic disease that has substantial physical and emotional impact on patients



Emotional burden[16,17]

- Depression
- Anxiety
- Parental guilt
- Fear

Renal manifestations[18,19]

- Hypertension
- Pain
- Kidney stones
- Recurrent UTIs
- Frequent urination
- Blood in urine

Extra-renal manifestations[6,18-20]

- Pancreatic and hepatic cysts
- Heart disease
- Hernias
- Male infertility
- Brain aneurysms
- Diverticulosis
- Tumors within pancreatic duct

Diagnosis and monitoring ADPKD

Multiple techniques can be used to confirm a diagnosis of ADPKD

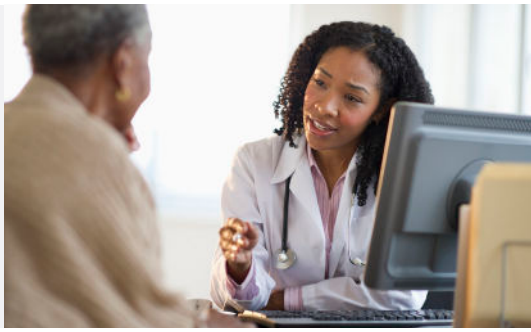
Positive family history and genetic testing[15]

- The variable symptoms of ADPKD can make confirming a positive family history challenging.[15]
- Genetic testing is available to help confirm a diagnosis of ADPKD.[15]

Imaging studies including ultrasonography, computed tomography, and magnetic resonance imaging (MRI)[15,21]

- While ultrasonography is a safe, easily performed, inexpensive, and most commonly used imaging tool to diagnose ADPKD, it is not precise enough to detect short-term disease progression.[22]
- MRI has been shown to be more sensitive and reliable for measurement of renal cyst volume.[22]

Because the rate at which **ADPKD advances** can be variable, **monitoring progression is one way to help manage the disease**.[4]



The benefits of early intervention

Earlier detection and management of ADPKD may provide the opportunity for interventions to treat early-onset hypertension and cardiovascular complications, cyst infection, and nephrolithiasis.[15,22]

While symptoms may be fewer in early-stage disease, the kidneys continue to increase in volume and damage continues to progress.[4,23]

By the time serum creatinine levels start to rise appreciably, more than **50% of functional renal tissue** may have already been destroyed.[24]

Considerations for the Healthcare Team

Considerations when measuring disease progression

For patients in earlier stages of the disease, measuring estimated glomerular filtration rate (eGFR) may not reveal the ongoing damage caused by ADPKD.[24]

- eGFR and serum creatinine levels are important indicators of kidney function but alone may not be reliable indicators of early-stage ADPKD.[25]
- eGFR may remain steady over many years while the kidneys increase in volume by 400 percent, to 1500 cm^3.[4]

Compensatory renal hypertrophy and glomerular hyperfiltration can mask the underlying destruction of the surrounding renal parenchyma.[26,27]

Serum creatinine levels rise late in the course of the disease, only after the parenchyma has incurred serious, irreversible damage.[24]

An increase in total kidney volume (TKV) can precede a drop in eGFR levels.[24,28,29]

The role of total kidney volume

TKV can provide an important predictor of early-stage disease progression and future renal decline even before eGFR levels begin to drop. TKV provides an indicator of progression in early-stage ADPKD, as it can be used to evaluate patients with normal eGFR levels.[24,28,29]

In 2016, the FDA provided a recommendation for the use of TKV, measured at baseline, as a prognostic enrichment biomarker to select patients with ADPKD at high risk of a progressive decline in renal function.[30]

Managing ADPKD*

Stages of chronic kidney disease[31*]

Staging of chronic kidney disease based on GFR category

CKD Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with **normal** or elevated	**≥90**
2	Kidney damage with **mildly decreased**	**60-89**
3	**Moderately decreased**	**30-59**
4	**Severely decreased**	**15-29**
5	Kidney **failure**	**<15** (or dialysis)

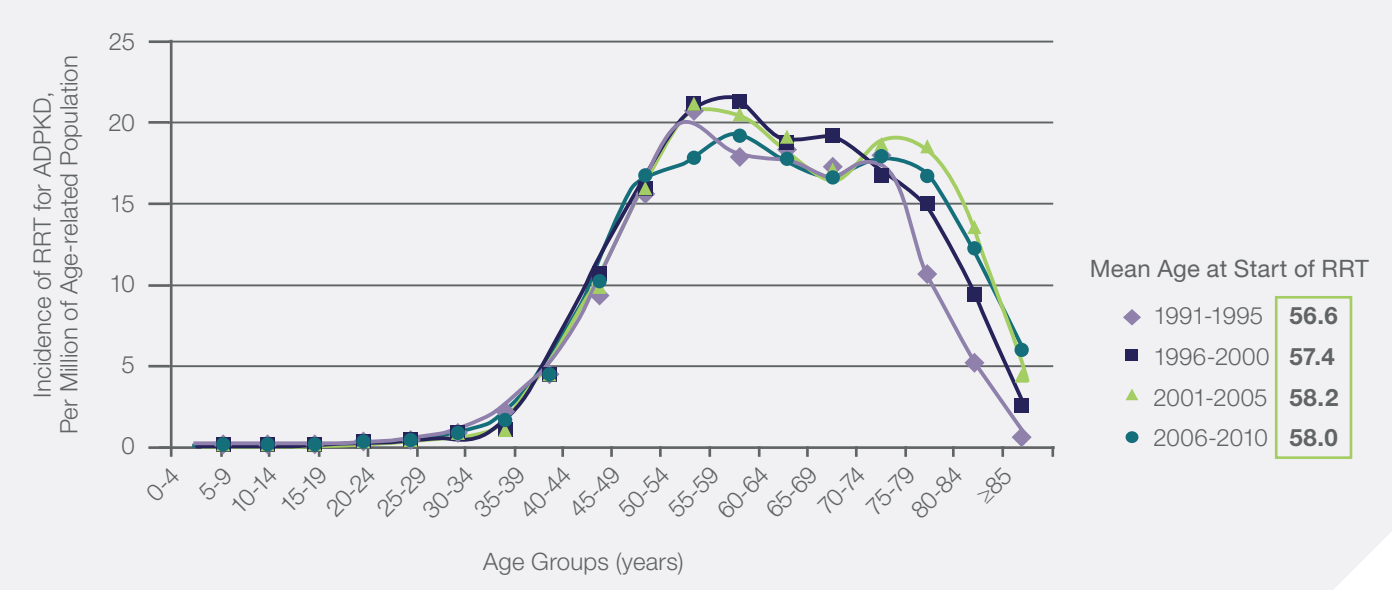
*Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.[31]

If you are a primary care physician managing early-stage ADPKD patients, it may be important to refer them to a nephrologist.

Considerations for the Healthcare Team

Outcomes for patients with ADPKD have not changed in decades

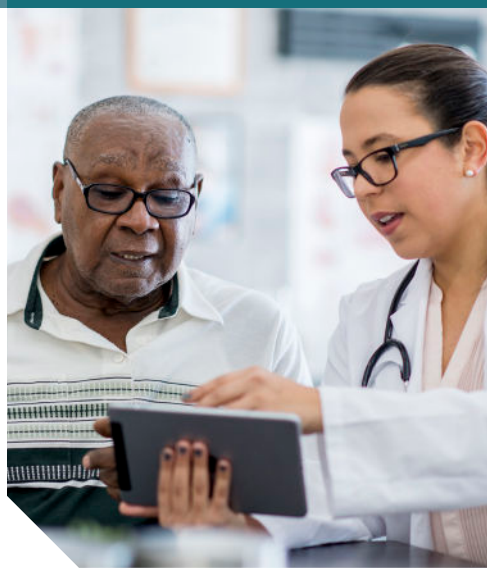
Despite aggressive symptomatic treatment, incidence of renal replacement therapy (RRT) has not changed in over 20 years.[32]



Management strategies are similar to those for CKD

Because there are currently no evidence-based guidelines in the United States specific to the care of patients with ADPKD, healthcare providers may consult guidelines developed for the broader population of patients with CKD.[33]

	CKD Stage				
	1	2	3	4	5
GFR and electrolytes	Annually		Every 6-12 months	Every 3-6 months	Every 1-3 months
Assessment for proteinuria	Annually		Every 6-12 months	Every 3-6 months	
Blood pressure	Every visit				
Calcium and phosphate	Annually			Every 3-6 months	
Parathyroid hormone	—		Annually	Every 3-6 months	
Hemoglobin	Annually			Every 3-6 months	Every 1-3 months



Identification of patients at risk for rapid progression may provide an opportunity for intervention[25,27,34]

Risk factors associated with rapid disease progression

- TKV greater than expected for age[35-37]
- Truncating PKD1 mutation[38]
- Family history of ESRD at or before age 58[39]
- Hypertension before age 35[34,38]
- Urologic events before age 35[38]
  - Gross hematuria
  - Cyst infection
  - Flank pain related to cysts
- Male gender[38]
- eGFR decline[39]
  - ≥5 mL/min/1.73 m^2 within one year

Treatment strategies have focused on symptom control

Treatment has focused on reducing morbidity and mortality from the complications of the disease. Ways to manage the disease include[18]:

Standard care

- Blood pressure control
- Managing pain
- Antibiotics for UTIs
- Dialysis
- Renal transplantation

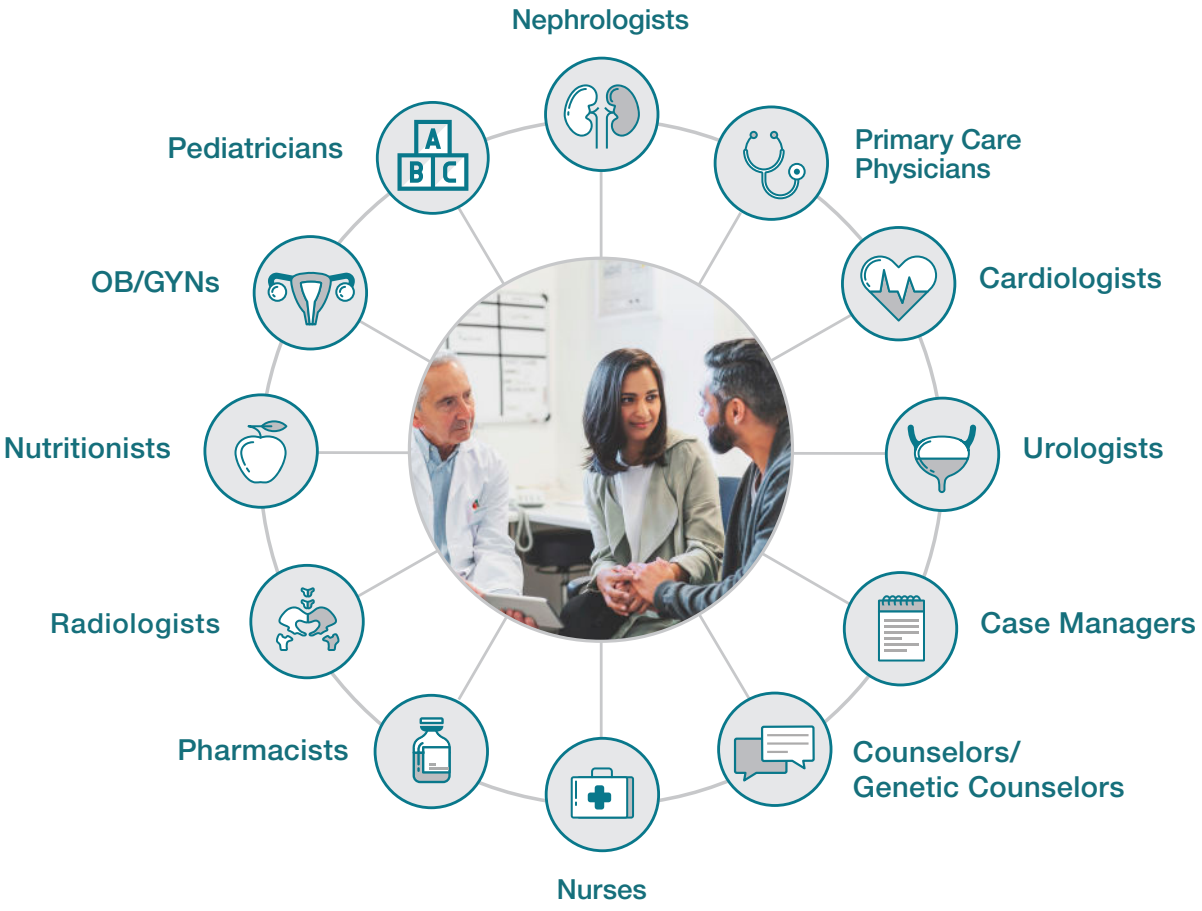
Lifestyle approaches

- Increasing water intake
- Dietary restrictions
  - Salt restriction
  - Low protein intake
- Avoidance of caffeine and smoking
- Regular exercise
- Maintenance of healthy body weight

Consider tailoring the frequency of monitoring to the needs of the patient and based on the judgment of the treating healthcare professional.

ADPKD provides the opportunity for a patient-centered interdisciplinary approach

Due to the systemic nature of ADPKD, the opportunity for collaboration among interdisciplinary teams exist. Healthcare providers involved in management of patients with APDKD include:



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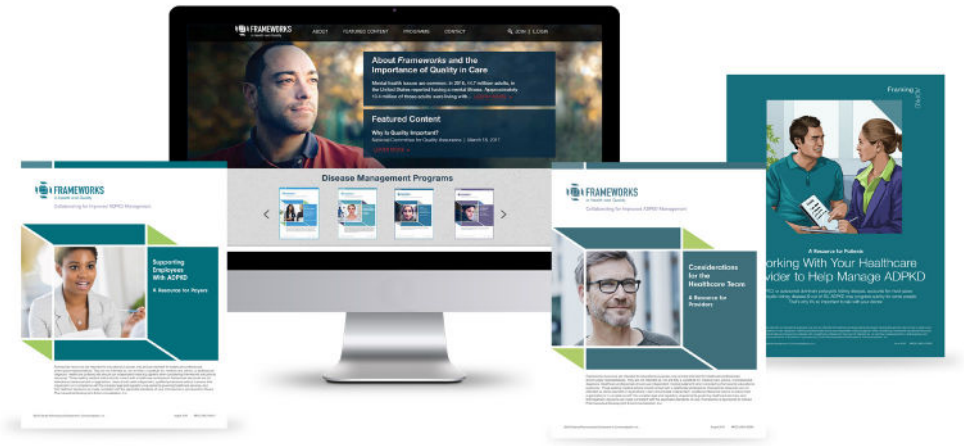
Collaborating for improved ADPKD management

As part of our dedication to providing you leading ADPKD education, Otsuka Pharmaceutical Development & Commercialization, Inc. is pleased to offer the *Frameworks in Health and Quality: Collaborating for Improved ADPKD Management*, a disease management program supporting payers, healthcare providers, and patients and their caregivers.

Program objectives:

- Emphasize the importance of understanding ADPKD and its impact for patients.
- Enhance communication among all stakeholders with emphasis on interdisciplinary collaboration.
- Support stakeholders with provider, patient, and caregiver educational materials.
- Promote ADPKD topics such as management, monitoring for progression, and patient engagement.



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