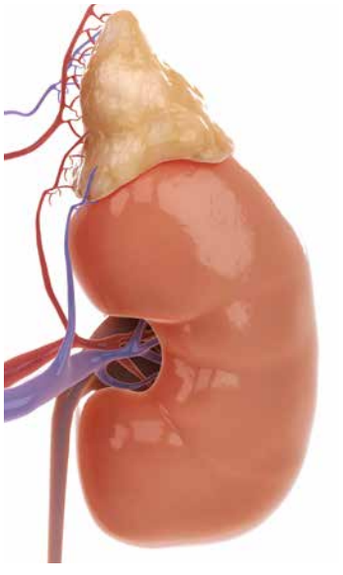
GENERAL PRACTITIONER'S GUIDE
TO UNDERSTANDING ADPKD

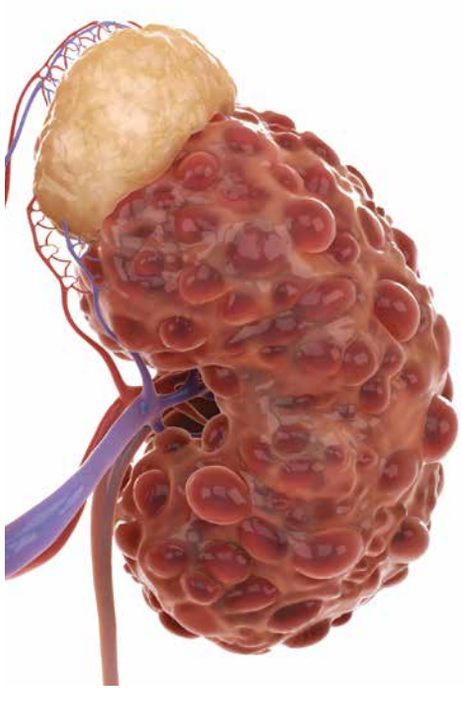
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

A PROGRESSIVE DISEASE THAT STARTS BEFORE SYMPTOMS APPEAR[1,2]

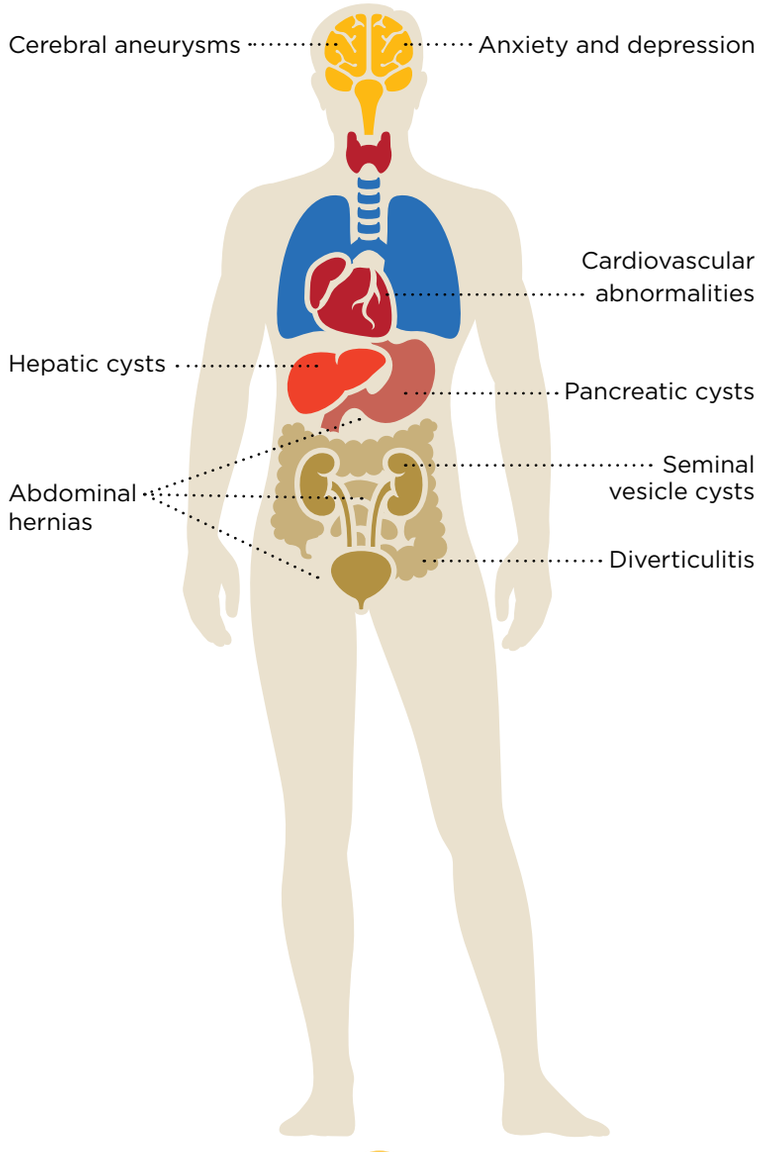
WHAT IS ADPKD?

- The most common inherited renal disorder, with a prevalence of 1:400 to 1:1,000[2,3]
  - Equates to 35,000-70,000 Canadians
- Characterized by relentless development and growth of bilateral renal cysts causing progressive kidney enlargement associated with:[4]
  - Early onset hypertension
  - Abdominal fullness and pain
  - Episodes of cyst hemorrhage
  - Urinary tract infections
  - Gross hematuria
  - Nephrolithiasis
  - Cyst infections
  - Reduced quality of life
  - Progressive renal failure[1]





Extrarenal complications[1,4-6]



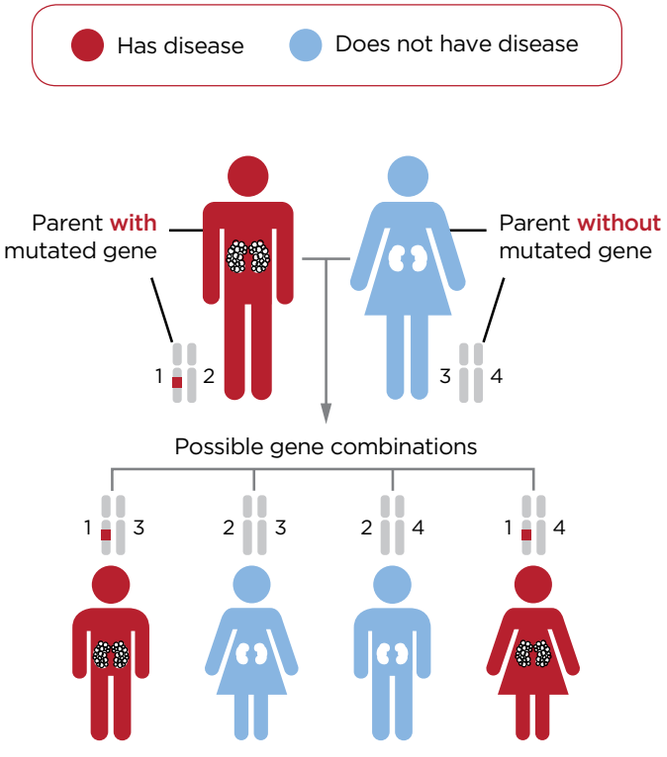
YOU MAY ALREADY HAVE A PATIENT WITH ADPKD!

Including undiagnosed cases, ADPKD is more prevalent than Huntington's disease, sickle cell disease, cystic fibrosis, myotonic dystrophy, and hemophilia combined.[3,7]

WHAT CAUSES ADPKD?[1,2,7]

- ADPKD is caused by a heterozygous mutation in one of two genes:
  - Mutations in the *PKD1* gene occur in 80% to 85% of cases of ADPKD
    - Patients with *PKD1* tend to progress to ESRD earlier (mid-50s vs. mid-70s) and have a larger number of renal cysts
  - Mutations in the *PKD2* gene account for the remainder of cases
  - *De novo* spontaneous mutations account for approximately 6% to 8% of cases
  - A positive family history is absent in 10-15% of patients

ADPKD is an autosomal dominant disease

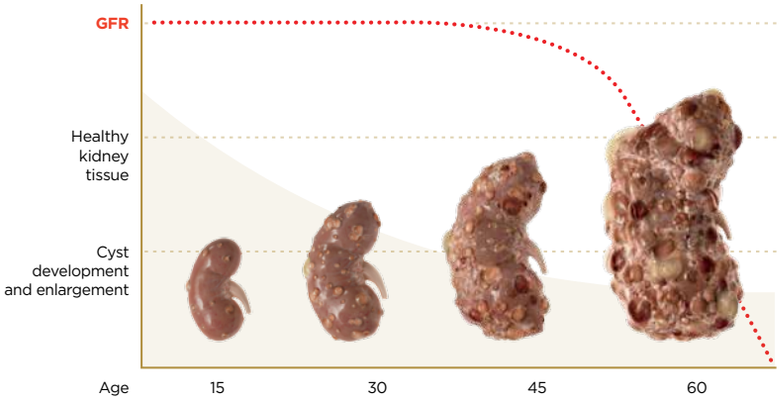


50% RISK OF PASSING THE CONDITION ON TO OFFSPRING

ADPKD STARTS BEFORE SYMPTOMS APPEAR[1,2]

- Patients are commonly asymptomatic at the time of diagnosis.[1]
- Cyst growth displaces and destroys normal kidney tissue, culminating in fibrosis, renal architectural derangement, and ultimately kidney failure.[2,4]
- Glomerular filtration rate (GFR) and kidney function remain stable for several decades (despite a significant cyst burden) due to compensatory hyperfiltration of a subset of nephrons and are therefore not informative for indicating disease progression.[1,8]
  - Compensatory hyperfiltration in surviving nephrons initially maintains serum creatinine levels at or near normal values; when levels start to rise appreciably above baseline, more than 50% of functioning parenchyma has been destroyed.[9]

Cysts cause renal parenchymal damage years before GFR begins to decline[8,10]



– Adapted from Grantham *et al.* (2011)[8] and Grantham *et al.* (2006)[10]

TOTAL KIDNEY VOLUME (TKV)[4,7,11]

In the early stages of disease, there is little change in kidney function yet detectable changes in total kidney volume. Therefore, kidney function by itself is not informative.

TKV is a more sensitive measure of disease progression than kidney function. TKV in relation to age can identify patients with progressive disease. It increases exponentially in virtually every ADPKD patient with an average of **5-6% per year** in adults.

CRITERIA FOR ULTRASONOGRAPHIC DIAGNOSIS OF ADPKD[12]

Individuals who are at risk for ADPKD are often screened by ultrasound. In individuals of unknown genotype, the following criteria are sufficient for establishing a diagnosis:

15-39 years old	Three or more (unilateral or bilateral) renal cysts
40-59 years old	Two or more cysts in each kidney
≥60 years	Four or more cysts in each kidney

Conversely, fewer than two renal cysts in at-risk individuals aged 40 years is sufficient to exclude the disease.

Note that the criteria are valid only in patients with a family history of ADPKD and are specific for ultrasound imaging only.

CHECKLIST: WHAT TO DO WITH A NEWLY DIAGNOSED PATIENT

- ✓ Refer the patient to a nephrologist
- ✓ Assess family history (age at diagnosis and age at ESRD of other family members with ADPKD)
- ✓ Assess undiagnosed family members

WHEN TO REFER TO A NEPHROLOGIST

1. At first diagnosis

- All patients with a new diagnosis of ADPKD or uncertainty of the nature of their cystic kidney disease should be referred to a nephrologist for assessment. This will enable evaluation for complications (intracranial aneurysm, polycystic liver disease) of ADPKD and facilitate discussion about risk to the extended family (including children), which may require multidisciplinary input.[7]
- There is an unmet need for all ADPKD patients to have access to nephrologists knowledgeable about the disease.[4]

2. Throughout the course of disease

- Because ADPKD starts before symptoms appear,[1,2] the patient should have access to a multidisciplinary team, including a nephrologist, throughout the course of the disease.[4]

KEY TAKEAWAYS

- ADPKD is an autosomal dominant disease characterized by bilateral renal cysts and other extrarenal complications.[4]
- It is the most common inherited renal disorder, so you may already have a patient with ADPKD.[2,3]
  - Including undiagnosed cases, ADPKD is more prevalent than Huntington's disease, sickle cell disease, cystic fibrosis, myotonic dystrophy, and hemophilia combined.[3,7]
- Renal parenchymal damage occurs years before GFR begins to decline, and kidney function may remain normal for several decades due to compensatory hyperfiltration of a subset of nephrons.[1,8,10]
  - TKV in relation to age is thus a more sensitive measure to identify patients with progressive disease.[4,7,11]
- Because ADPKD starts before symptoms appear,[1] the patient should have access to a multidisciplinary team (including a nephrologist) throughout the course of the disease.[4]

TALK TO YOUR OTSUKA REP FOR MORE INFORMATION.

References: 1. Halvorson CR *et al.* Polycystic kidney disease: inheritance, pathophysiology, prognosis, and treatment. *Int J Nephrol Renovasc Dis* 2010;3:69–83. **2.** Cabellon M. Cystic Disease of the Kidney. In: Windus, David, editor. Nephrology Subspecialty Consult 2nd edition. New York: Lippincott, Williams & Wilkins, 2008. **3.** Belibi FA, Edelstein CL. Novel targets for the treatment of autosomal dominant polycystic kidney disease. *Expert Opin Investig Drugs* 2010;19(3):315-28. **4.** 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(1):17-27. **5.** Bennet WM, Torres VE. Extrarenal manifestations of autosomal dominant polycystic kidney disease. Available at: http://www.uptodate.com/contents/extrarenal-manifestations-of-autosomal-dominant-polycystic-kidney-disease. Last accessed: December 2016. **6.** 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(5):531-7. **7.** Simms RJ. Autosomal dominant polycystic kidney disease. *BMJ* 2016;352:i679. **8.** Grantham JJ *et al.* Why kidneys fail in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol* 2011;7:556–66. **9.** Grantham JJ. Autosomal Dominant Polycystic Kidney Disease. *Ann Transplant* 2009;14(4):86-90. **10.** Grantham JJ, Chapman AB, Torres VE. Volume progression in autosomal dominant polycystic kidney disease: the major factor determining clinical outcomes. *Clin J Am Soc Nephrol* 2006;1(1):148-57. **11.** Chapman A *et al.* Kidney Volume and Functional Outcomes in Autosomal Dominant Polycystic Kidney Disease. *Clin J Am Soc Nephrol* 2012;7:479-86. **12.** Pei Y, Obaji J, Dupuis A *et al.* Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;20(1):205-12.

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