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# Thirteen Questions Answered for Managing Patients with the Most Common Hereditary Kidney Disease

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## Disclosures

**Wendy L. Wright, DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP,** has disclosed that she is on the advisory board for Merck, Pfizer, Sanofi for Vaccines, and Glaxo for Vaccines and Osteoarthritis; Indorsia for Insomnia and Bayer for Chronic Kidney Disease; as well as on the speakers bureau for Merck, Pfizer and Sanofi for Vaccines and Biohaven and AbbVie for Migraines.

**Kim Zuber, PA-C,** disclosed no relevant financial relationship or interest with a proprietary entity producing, marketing, reselling or distributing health care goods or services.

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This CME activity includes discussion about uses of medications outside of their approved labeling.

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## Learning objectives

| After attending this presentation, participants should be able to… |
| --- |
| Identify persons at high risk of ADPKD. |
| Conduct a diagnostic evaluation. |
| Initiate evidence-based therapy to slow the progression of ADPKD and treat extra-renal manifestations. |

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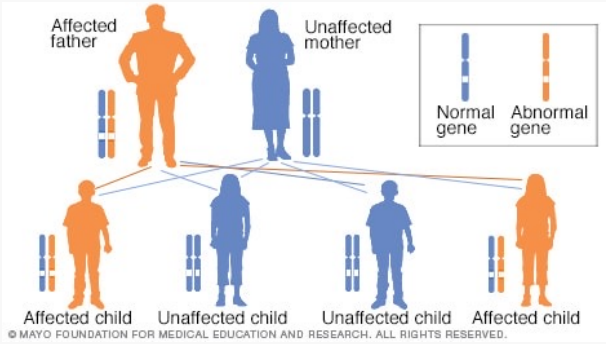
## What is ADPKD and why should I care?

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited form of kidney disease

Diagnosis usually occurs when patients are between the ages of 30 and 50

"Autosomal dominant"
The gene mutation can come from a single parent



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# 1. Which patients are at high risk of ADPKD?

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## Epidemiology of ADPKD

- Most common hereditary kidney disorder
  - Incidence: 1:400-1000 live births in US[1,2]
- Familial in a dominant Mendelian fashion
  - Carrier will pass down in a 1:1 fashion
  - 50% of all offspring will have ADPKD
- Due to mutations in *PKD1* and *PKD2* genes
  - Leads to very enlarged 'cystic' kidneys, livers
- More progressive in men than women (1.2 to 1.3)[1,2]

1. National Institute of Health. https://www.niddk.nih.gov/health-information/kidney-disease/polycystic-kidney-disease/autosomal-dominant-pkd. Accessed June 27, 2021. 2. Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24.

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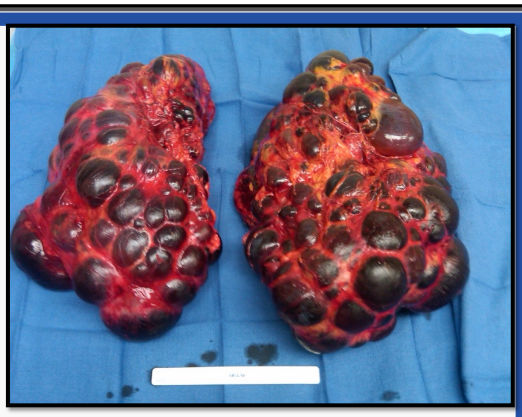
## Patient Presentation



- None
- Hypertension
- Hematuria
- Severe sharp low back pain
  - Due to burst cyst
  - May be found incidentally in r/o nephrolithiasis
- Hyperfiltration and thus eGFR may be 120+ until later in disease state
- Within a family, may have multiple presentations

1. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/polycystic-kidney-disease#statistics. Accessed March 18, 2020.
2. Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24.

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## Natural History

- Progressive development and enlargement of renal cysts → exponential increase in total kidney volume
  - Some polycystic kidneys are as large as a football and weigh up to 30 pounds each
- Due to compensatory mechanisms, normal kidney function is usually maintained for decades
- Kidney function often begins to decline during 4$^{th}$ decade following destruction of most nephrons → ESKD
- Every member of a family can present differently, making diagnosis difficult.

1. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/polycystic-kidney-disease#statistics. Accessed March 18, 2020.
2. Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24.

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# 2. What are the clinical features of ADPKD?

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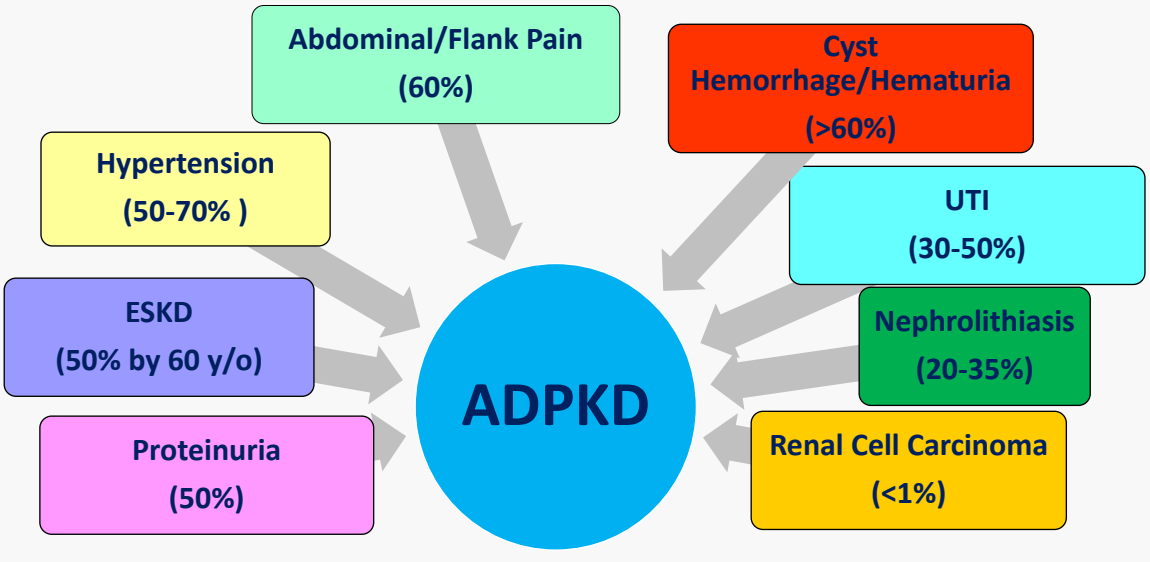
## Clinical presentation of ADPKD




Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24. Bhasin B, et al. *Am J Med Sci*. 2018;356(2):177-180. Ecder T. *Curr Hypertens Rev*. 2013;9(1):2-11. Nowak KL, et al. *Am J Kidney Dis*. 2019;74(2):213-223. Chebib FT, et al. *Am J Kidney Dis*. 2016;67(5):792-810. Chapman AB, et al. *Kidney Int*. 2015;88():17-27.

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Hypertension is likely to be the presenting sign in a patient with undisclosed ADPKD.

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## Diagnostic Evaluation (cont)

**History**

- If family history of ADPKD: number/relationship of family members; age at diagnosis; age at developing ESKD; known genetic mutations
- If no family history of ADPKD → look for a history of family with symptoms related to ADPKD

Chapman AB, et al. *Kidney Int.* 2015;88(1):17-27. Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24. Pei Y, et al. *J Am Soc Nephrol.* 2009;20(1):205-212. Cornec-Le Gall E, et al. *Lancet.* 2019;393(10174):919-935.

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# 3. What extra-renal complications are common?

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## Clinical Features: Extra-Renal Manifestations

| | |
|---|---|
| Polycystic liver disease | >80% by age 30 y |
| Intracranial aneurysm | 9% to 12% of adults (20% to 27% with family history of ICA) |
| Arachnoid cysts | 8% to 12% of adults |
| Mitral valve prolapse or bicuspid aortic valve | <25% of adults |
| Pericardial effusion | <35% of adults |
| Pancreatic cysts | 10% of adults |
| Diverticulosis | <50% with ESKD |
| Bronchiectasis | 35% to 40% of adults |
| Seminal vesicle cysts | <40% of men |

ESKD, end-stage kidney disease; ICA, intracranial aneurysm

Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24. Bhasin B, et al. *Am J Med Sci*. 2018;356(2):177-180. Ecder T. *Curr Hypertens Rev.* 2013;9(1):2-11. Nowak KL, et al. *Am J Kidney Dis*. 2019;74(2):213-223. Chebib FT, et al. *Am J Kidney Dis*. 2016;67(5):792-810. Chapman AB, et al. *Kidney Int*. 2015;88():17-27.

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# 4. What laboratory and radiologic testing is appropriate?

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## Diagnostic Evaluation (cont)

**History**

- If family history of ADPKD: number/relationship of family members; age at diagnosis; age at developing ESKD; known genetic mutations
- If no family history of ADPKD → look for a history of family with symptoms related to ADPKD

**Imaging**

- Ultrasound: generally used first due to low cost, widespread availability; less sensitive than MRI or CT
- If ultrasound positive → MRI or CT useful to determine prognosis
- If MRI/CT positive → nephrologist referral recommended

Chapman AB, et al. *Kidney Int.* 2015;88(1):17-27. Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24. Pei Y, et al. *J Am Soc Nephrol.* 2009;20(1):205-212. Cornec-Le Gall E, et al. *Lancet.* 2019;393(10174):919-935.

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The diagnosis of ADPKD is confirmed primarily by ultrasound.

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## Diagnosis Often Occurs During/As:

- Routine evaluation in asymptomatic patient with positive family history of ADPKD
- Incidental finding during an imaging study for pregnancy, trauma, surgery, or other unrelated reason
- Evaluation for hypertension
- Evaluation for hematuria, cyst rupture, kidney stones, or some other symptom related to ADPKD

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# 5. What is the role of genetic testing?

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## Diagnostic Evaluation (cont)

**History**
- If family history of ADPKD: number/relationship of family members; age at diagnosis; age at developing ESKD; known genetic mutations
- If no family history of ADPKD → assess for other acquired disorders

**Imaging**
- Ultrasound: generally used first due to low cost, widespread availability; less sensitive than MRI or CT
- If ultrasound positive → MRI or CT useful to determine prognosis
- If MRI/CT positive → nephrologist referral recommended

**Genetic Testing**
- Usually limited to mild disease manifestations, atypical presentation, presence of a few cysts but negative family history, to rule out ADPKD in a young potential kidney donor, or reproductive counseling

Chapman AB, et al. *Kidney Int.* 2015;88(1):17-27. Bergmann C, et al. *Nat Rev Dis Primers*. 2018;4(50):1-24. Pei Y, et al. *J Am Soc Nephrol.* 2009;20(1):205-212. Cornec-Le Gall E, et al. *Lancet.* 2019;393(10174):919-935.

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# 6. How is prognosis determined?

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## Prognosis

- Goal is to identify patients at high risk of CKD progression
- Serum creatinine, blood urea nitrogen often remain normal until 4th decade of life
- Risk assessment
  - PROPKD score[1]
    - Based on gender, hypertension onset before age 35 y, urologic complications before age 35 y, and genotype
  - Mayo classification system[2]
    - Based on age, height, total kidney volume, coronal image of kidneys
    - Total kidney volume calculator
      - https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754
    - Allows estimation of future eGFR
    - Not applicable to 5% with atypical presentation

1. Cornec-Le Gall E, et al. *J Am Soc Nephrol.* 2016;27(3):942-951.
2. Irazabal MV, et al. *J Am Soc Nephrol.* 2015;26(1):160-172.

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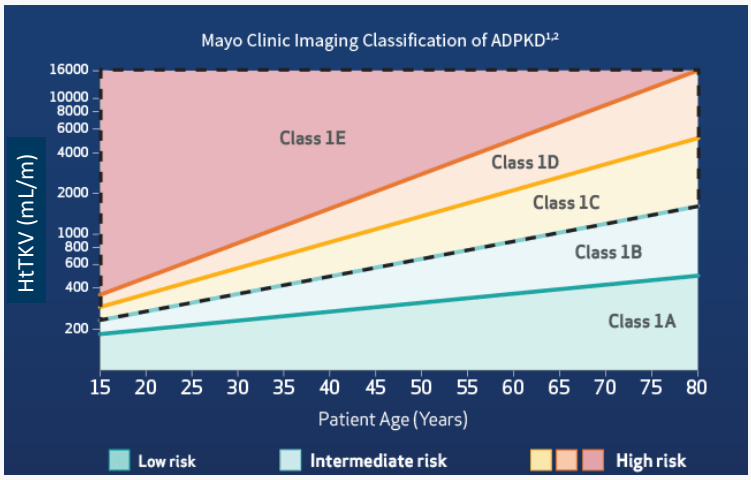
# Mayo Classification System




| ΔhtTKV | <1.5% | 1.5-3% | 3-4.5% | 4.5-6% | ≥6% |
|---|---|---|---|---|---|
| Class | 1A | 1B | 1C | 1D | 1E |

HtTKV, height-adjusted total kidney volume


Irazabal MV, et al. *J Am Soc Nephrol.* 2015;26(1):160-172.

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# 7. What are the treatment goals?

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## Treatment Goals

- Slow disease progression
- Reduce need for kidney replacement therapy
- Reduce patient burden of disease
  - Psychological/Quality of life
  - Physical - pain, abdominal fullness, cardiovascular disease, urinary complications

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## 8. What basic medical treatment should be offered to all patients to slow the progression of ADPKD?

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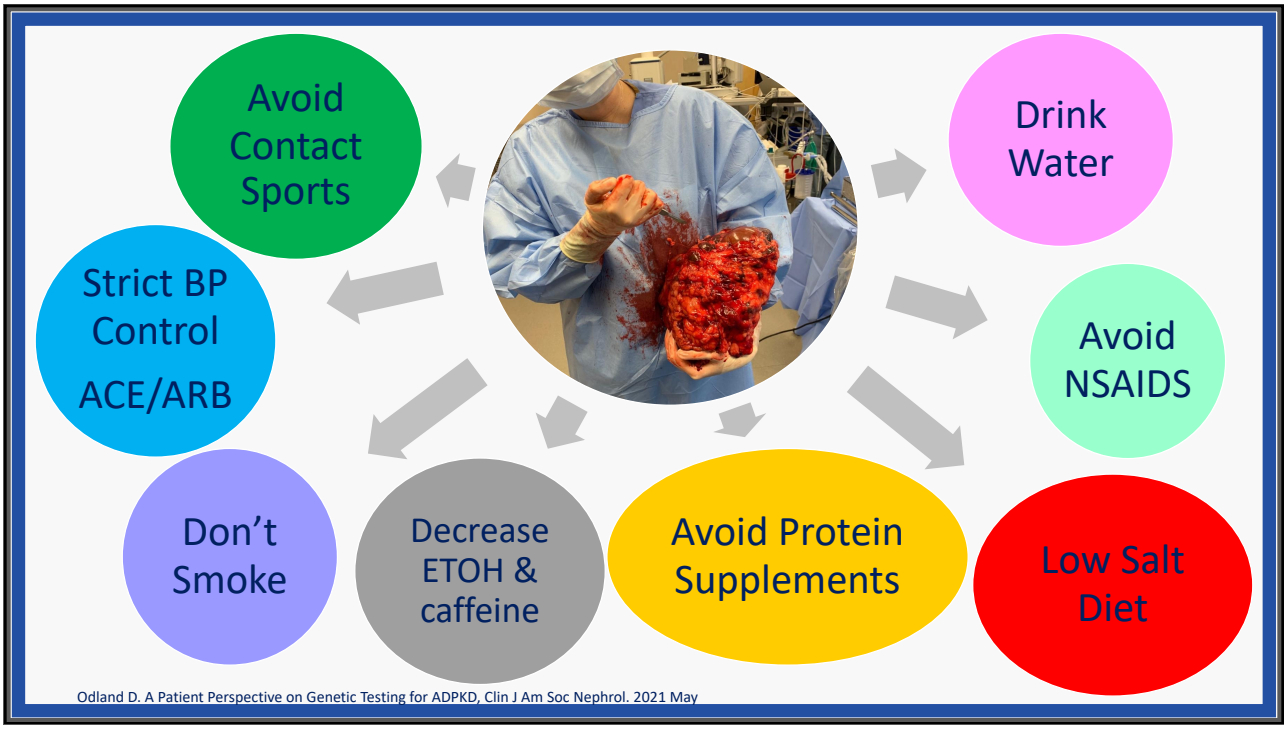


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## Angiotensin Blockade in ADPKD: HALT-PKD

- Adults with ADPKD and eGFR>60 mL/min/1.73 $m^2$
- Randomized (1:1) to:
  - Lisinopril + telmisartan
  - Lisinopril + placebo
  - Adjusted to achieve BP 110/70 to 130/80 mm Hg
- 5- to 8-y treatment

TKV= total Kidney Volume

| | ACE + Placebo | ACE + ARB |
|---|---|---|
| **Strict BP 110/70** | Dec TKV, no chg eGFR | Dec TKV, no chg eGFR |
| **Standard BP 130/80** | No chg TKV No chg eGFR | No chg TKV No chg eGFR |

HALT-PKD showed early aggressive BP management in **EARLY** disease will slow cyst growth

TSchrier RW, et al. Blood pressure in early autosomal dominant polycystic kidney disease. N Engl J Med, . 2014 Dec 11;371(24):2255-66.

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## Key Treatment Issues

- Blood pressure
  - Achieving BP 95-110/60-75 mmHg superior to 120-130/70-80 mmHg in slowing increase in TKV (no impact on eGFR)
  - HTN in a teen (adjusted for age/height/weight) SHOULD be treated
- Pain
  - Acute- kidney cyst hemorrhage; infection; stones
  - Chronic- stretching/pulling of kidney capsule; back pain
  - Use caution with NSAIDS, opioid medications
- Pregnancy
  - Caution with exogenous estrogen, progesterone
  - Family planning- genetic counseling

TKV, total kidney volume

Schrier RW, et al. *N Engl J Med.* 2014;371(24):2255-2266. Brosnahan GM, et al. *Curr Hypertens Rev.* 2018;14(1):39-47.

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## 9. What evidence-based medications are available to slow progression of kidney disease in patients with ADPKD?

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## Medications to Slow Progression of Kidney Disease in ADPKD

| FDA Approved for ADPKD | Investigational Medications |
|---|---|
| Tolvaptan | Somatostatin/Analogs<br>• Somatostatin<br>• Octreotide<br>• Lanreotide<br>mTOR inhibitor<br>• Rapamycin<br>• Everolimus<br>Amiloride<br>Renin-angiotensin-aldosterone inhibitor |

ACE/ARB therapy is known to slow progression of kidney disease but is not specific to ADPKD.

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## Tolvaptan – The Only Medication Approved by FDA for ADPKD

- Pathophys/MOA
- Vasopressin V2-receptor antagonist

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# 10. Which patients should be treated with tolvaptan?

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## Patient Selection

- Approved indication[1]
  - Tolvaptan is indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD
- Adults at risk of rapid disease progression
  - Mayo classes 1C, 1D, 1E
- Most experience in adults age ≤55 y and eGFR ≥25 mL/min/1.73 $m^2$
- Available only through REMS program

1. Jynarque [package insert]. Rockville, MD: Otsuka Pharmaceuticals, Inc.; October 2020.

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## Patient Selection

- Key contraindications
  - History of significant liver injury/impairment (excluding uncomplicated polycystic liver disease)
  - Concomitant use of strong CYP3A4 inhibitors
  - Uncorrected abnormal blood $Na^+$
  - Unable to sense or respond to thirst
  - Hypovolemia
  - Uncorrected urinary outflow obstruction
  - Anuria

Jynarque [package insert]. Rockville, MD: Otsuka Pharmaceuticals, Inc.; October 2020.

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## 11. What are the expected benefits with tolvaptan?

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# Tolvaptan in Early-Stage ADPKD: TEMPO 3-4

- Adults with ADPKD
  - TKV ≥750 mL
  - CrCl ≥60 mL/min
- Randomized (2:1) to:
  - Tolvaptan (titrated to 90 mg qAM and 30 mg qPM based on tolerability)
  - Placebo
- 3-y treatment

CrCl, creatinine clearance; TKV, total kidney volume

Torres VE, et al. *N Engl J Med*. 2012;367(25):2407-2418.

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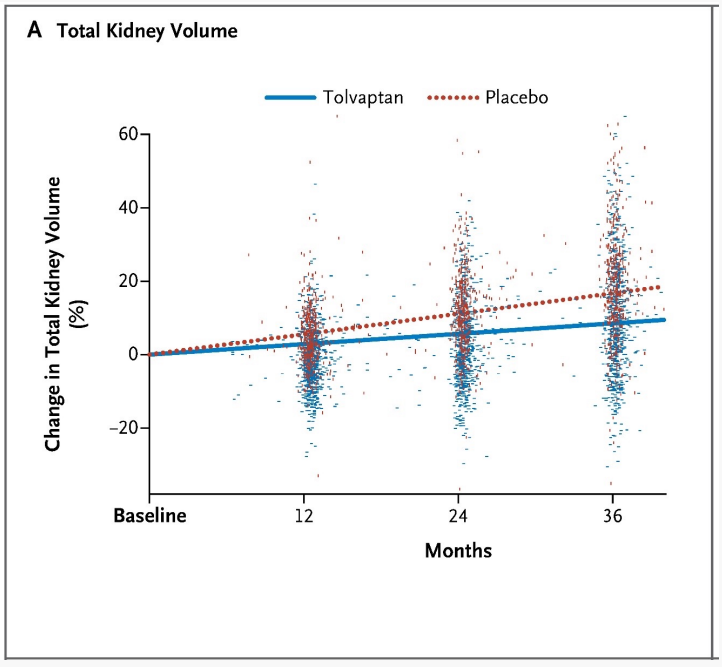
# Tolvaptan in Early-Stage ADPKD: TEMPO 3-4

**High risk patients should be treated early and aggressively.**




From The New England Journal of Medicine, Torres VE, et al for the TEMPO 3:4 Trial Investigators. Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease. Volume 367, pages 2407-2418. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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# Tolvaptan in Early-Stage ADPKD: TEMPO 3-4

| Adverse Events More Common in Tolvaptan Group (*P*<0.05) | Tolvaptan (n=961) | Placebo (n=483) |
|---|---|---|
| Thirst | 55.3% | 20.5% |
| Polyuria | 38.3% | 17.2% |
| Nocturia | 29.1% | 13.0% |
| Urinary frequency | 23.2% | 5.4% |
| Polydipsia | 10.4% | 3.5% |
| Discontinued treatment | 23% | 14% |
| Discontinued treatment due to adverse event* | 15.4% | 5.0% |

*Primarily related to aquaresis (thirst, polyuria, nocturia, polydipsia) and increases in liver enzymes >3 times upper limit

Torres VE, et al. *N Engl J Med*. 2012;367(25):2407-2418.

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# 12. What education should be provided to patients treated with tolvaptan to optimize its use?

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## Patient Education

- Take first dose upon awakening (with/without food); 2nd dose 8 hours later
- Pregnancy/Breastfeeding: not recommended
- Most common adverse events:
  - Thirst, polydipsia, polyuria, urinary frequency
  - Drink water to avoid thirst, dehydration
- Avoid coadministration with:
  - moderate/strong CYP3A4 inhibitors, eg, ketoconazole, itraconazole, fluconazole, lopinavir/ritonavir, ritonavir, conivaptan
  - moderate/strong CYP3A4 inducers, eg, grapefruit juice, rifampin
  - V2 agonist, ie, desmopressin
- REMS program

Jynarque [package insert]. Rockville, MD: Otsuka Pharmaceuticals, Inc.; October 2020.

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## 13. How might the primary care clinician and nephrologist collaborate?

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# Role of Primary Care Clinician

- Diagnosis – remember that a family history without specific ADPKD diagnosis, but the presence of many related symptoms, should cause suspicion.
- Clinical manifestations are the principal target in ongoing management
- Common renal manifestations are best recognized and managed early → primary care setting
  - Pain, hematuria, infection, nephrolithiasis
- A multidisciplinary approach is preferred.

Harris T, et al. *Nephrol Dial Transplant*. 2018;33(4):563-573.

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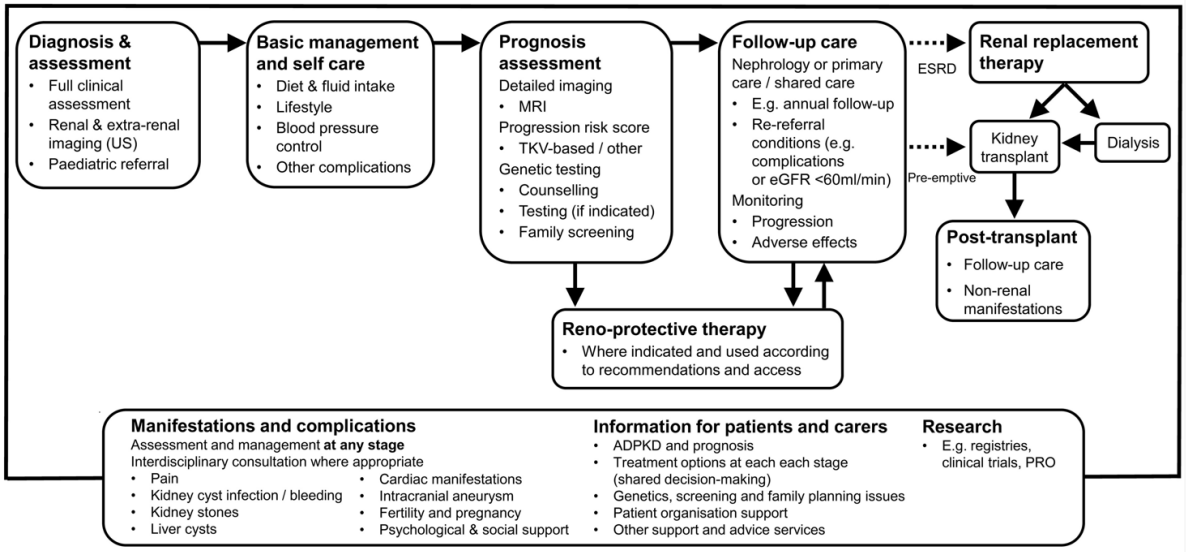
# ADPKD Care Pathway




ESRD, end-stage renal disease; eGFTestimated glomerular filtration rate, MRI, magnetic resonance imaging; PRO, patient-reported outcome, TKV, total kidney volume


Harris T, et al. *Nephrol Dial Transplant*. 2018;33(4):563-573.

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# Thirteen Questions Answered for Managing Patients with the Most Common Hereditary Kidney Disease

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