Identify appropriate patients with ADPKD for JYNARQUE® (tolvaptan), like Tim

Tim, 31—Stage 2 CKD

Tim works from home as a sales manager for a technology company. Lately, he's been taking online classes to learn to play drums.

Even though Tim had a relatively stable eGFR, his family history of early ESKD led his nephrologist to scan his kidneys for a TKV measurement.

Physical Findings and Labs:

- **Age:** 31 • **Height:** 5'11" • **Weight:** 180 lbs • **BMI:** 25
- **BP:** 107/73 mm/Hg, controlled on an ARB therapy
- **Creatinine:** 1.4 mg/dL
- **Current eGFR:** 67 mL/min/1.73 m^2
  - **eGFR:** 70 mL/min/1.73 m^2 1 year ago
- **htTKV:** 583 mL/m
- **Mayo Imaging Classification:** 1C (high risk) **Click here for TKV calculation.**

Medical History:

- Diagnosed with ADPKD as a young adult when an ultrasound showed innumerable, bilateral cysts
- Kidney stones

Family History:

- Father, uncle, and brother diagnosed with ADPKD
- Father developed ESKD at age 54
- Uncle received a kidney transplant at age 50

Patient image and patient case are fictional.

ADPKD=autosomal dominant polycystic kidney disease; ARB=angiotensin II receptor blockers; BMI=body mass index; BP=blood pressure; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; TKV=total kidney volume.

JYNARQUE®
(tolvaptan)
15, 30, 45, 60, 90 mg tablets

INDICATION:

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

WARNING: RISK OF SERIOUS LIVER INJURY

- **JYNARQUE® (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported**
- **Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity**
- **Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the Tolvaptan for ADPKD Shared System REMS**

Please see **IMPORTANT SAFETY INFORMATION** on pages 5 and 6.

Calculating Tim's TKV

Tim's TKV can be calculated using measurements of kidney length, width, and depth with the ellipsoid equation.[1,2]

Left kidney **Right kidney**

$\pi/6 \cdot (L \times W \times D) + \pi/6 \cdot (L \times W \times D) = TKV\ (mL)$

Height-adjusted (ht) TKV

Tim's htTKV can be used to estimate his future renal decline.

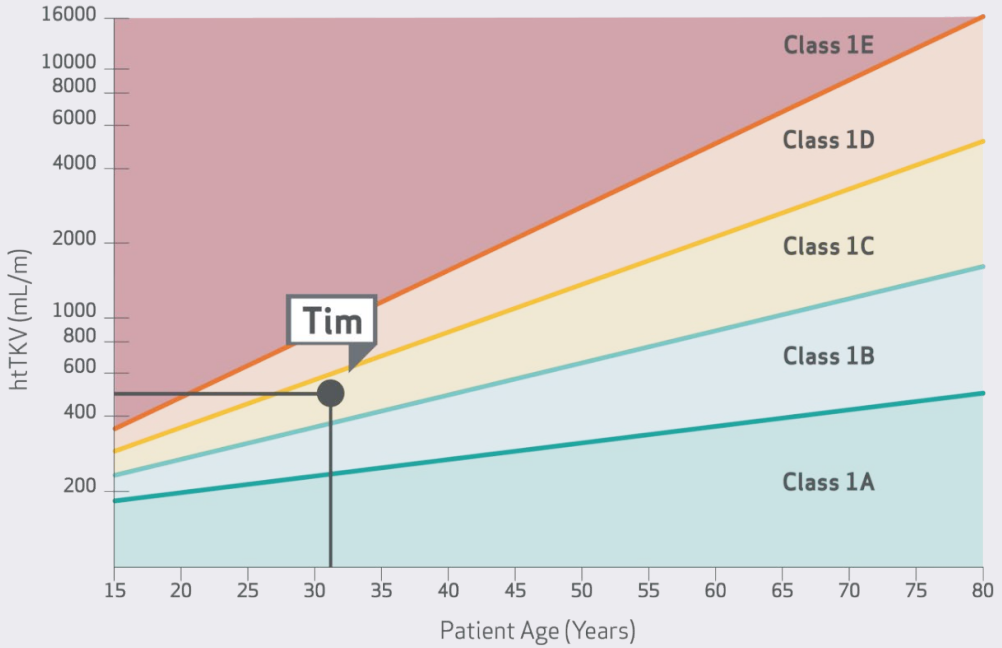
TKV/height (m) = htTKV (mL/m)

TKV: 1050 mL
Height: 1.8 m
Tim's htTKV: 583.33 mL/m

L=length; W=width; D=depth.

Units for kidney dimensions are in mm. To get kidney volume in mL, multiply by 0.001.

Plotting htTKV and age predicts the change in eGFR over time in patients with typical ADPKD[3*]



A patient's ADPKD imaging classification can help estimate their disease progression

Class	Estimated kidney growth rate: yearly percentage increase	Estimated slope of change in eGFR
1C	3.0% – 4.5%	-2.63

eGFR units=mL/min/1.73 m^2/yr.

Tim is Mayo Classification 1C

*Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV.

Republished with permission of the American Society of Nephrology, from Imaging classification of autosomal polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol*. 2015;26(1):160-172.

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Assessing ADPKD progression and treatment consideration

- Even though Tim had a relatively **stable eGFR**, his **family history of early ESKD** led his nephrologist to scan his kidneys for a **TKV measurement**
- His nephrologist knew that **CRISP data** show that a **one-time measurement of TKV** can help assess the rate of progression and **predict the rate of future kidney function decline**[4*]
- Given the **Mayo Imaging Classification of 1C**, Tim's nephrologist determined he was at **high risk for rapidly progressing ADPKD**[3]
- After further assessment, Tim's nephrologist determined he was an appropriate patient and recommended he start treatment with JYNARQUE® (tolvaptan)

*The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) is an NIH-funded, 14-year observational study (N=241) of adult ADPKD patients. The primary goal was to determine the extent to which TKV forecasts the development of renal insufficiency in ADPKD.[4,5]
NIH=National Institutes of Health.

SELECT IMPORTANT SAFETY INFORMATION:

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

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Starting JYNARQUE® (tolvaptan)

- Tim's nephrologist **explained the benefits and risks** associated with treatment, including the risk of serious liver injury, the requirements of the REMS program, and also reviewed the medication guide prior to starting treatment
- Tim had **additional questions about the risk of serious liver injury** and his nephrologist reviewed the incidence of liver injury observed during the clinical trials
  - 0.2% (3/1487) of JYNARQUE patients experienced serious hepatocellular injury in a 3-year placebo controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months) compared to none of the placebo-treated patients
  - In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9% [80/1637] versus 1.1% [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug
- Tim's nephrologist noted that Otsuka has a plan in place to help **facilitate REMS compliance** during the COVID-19 pandemic
- Tim's nephrologist explained that JYNARQUE may cause aquaretic side effects and advised him to **drink more water to avoid thirst and dehydration**
- Based on Tim's commercial insurance coverage, his specialty pharmacy determined he was eligible for **$10/month copay support***

*Assumes one 28-day supply prescription per month. If more than one prescription is filled in a calendar month, patients may pay more than $10 in that month. Other terms and conditions may apply.
ALT=alanine transaminase; REMS=Risk Evaluation and Mitigation Strategy; ULN=upper limit of normal.

SELECT IMPORTANT SAFETY INFORMATION:

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

References: 1. Magistroni R, Corsi C, Martí T, Torra R. A review of the imaging techniques for measuring kidney and cyst volume in establishing autosomal dominant polycystic kidney disease progression. *Am J Nephrol*. 2018;48:67-78. **2.** 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(3):479-486. **3.** 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(1):160-172. **4.** Yu ASL, Shen C, Landsittel DP, et al; for the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). Long-term trajectory of kidney function in autosomal-dominant polycystic kidney disease. *Kidney Int*. 2019;95(5):1253-1261. **5.** Chapman AB, Guay-Woodford LM, Grantham JJ, et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. *Kidney Int*. 2003;64(3):1035-1045. **6.** Gansevoort RT, Arici M, Benzing T, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrol Dial Transplant*. 2016;31(3):337-348. **7.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Intern Suppl*. 2013;3(1):1-150.

Please see **IMPORTANT SAFETY INFORMATION** on pages 5 and 6.

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INDICATION and IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan)

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- **JYNARQUE® (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported**
- **Measure transaminases (ALT, AST) and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity**
- **Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy program called the Tolvaptan for ADPKD Shared System REMS**

CONTRAINDICATIONS:

- History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease
- Taking strong CYP3A inhibitors
- With uncorrected abnormal blood sodium concentrations
- Unable to sense or respond to thirst
- Hypovolemia
- Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product
- Uncorrected urinary outflow obstruction
- Anuria

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

Please see **FULL PRESCRIBING INFORMATION**, including **BOXED WARNING**.

(continued on next page)

IMPORTANT SAFETY INFORMATION for JYNARQUE® (tolvaptan) (cont'd)

Hypernatremia, Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypernatremia. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure. Use with strong CYP3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients taking moderate CYP3A inhibitors. Patients should avoid grapefruit juice beverages while taking JYNARQUE.

Adverse Reactions: Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia.

Other Drug Interactions:

- **Strong CYP3A Inducers:** Co-administration with strong CYP3A inducers reduces exposure to JYNARQUE. Avoid concomitant use of JYNARQUE with strong CYP3A inducers
- **V_2-Receptor Agonist:** Tolvaptan interferes with the V_2-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V_2-agonist

Pregnancy and Lactation: Based on animal data, JYNARQUE may cause fetal harm. In general, JYNARQUE should be discontinued during pregnancy. Advise women not to breastfeed during treatment with JYNARQUE.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

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Talk to your sales representative or visit JYNARQUEhcp.com to learn more about appropriate patient types for JYNARQUE® (tolvaptan)

Tim, 31—Stage 2 CKD

Mayo Classification of 1C (high risk) and TKV greater than expected for his age point to risk of rapidly progressing ADPKD[3]

Julia, 40—Stage 2 CKD

Multiple risk factors as well as her concerning kidney length are signs of risk of rapidly progressing ADPKD[1,6]

Patient images and patient cases are fictional.

TKV=total kidney volume.

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