# Management of autosomal dominant polycystic kidney disease in the era of disease-modifying treatment options

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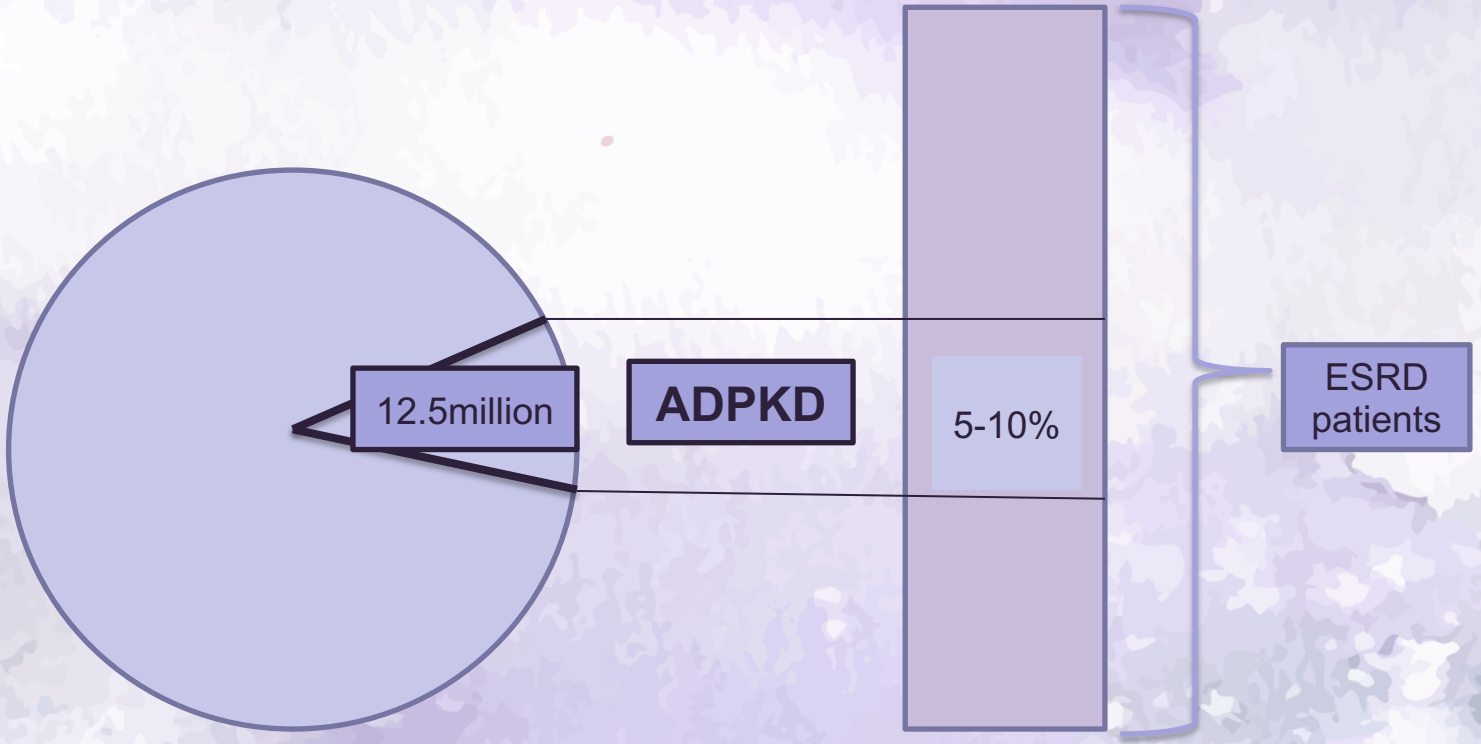
# Outlines

Epidemiology
Genetics and diagnosis
Prognosis
Kidney manifestation
CKD management

# Prevalence of ADPKD



# Genetic variability in ADPKD

Mutations in:

-*PKD1* gene —ON→ chromosome 16

g —Encoding→ polycystin (PC)-1

78%

-*PKD2 gene* —ON→ chromosome 4

i —Encoding→ PC-2

15%

-Minor ADPKD loci

# Genetic variability in ADPKD

- People who have an ADPKD or ADPLD spectrum phenotype but **have not been genetically screened** will continue to be termed ADPKD or ADPLD.

- People with ADPKD or ADPLD who have been **genetically tested** but in whom a **genetic diagnosis was not made** will continue to be termed ADPKD or ADPLD.

# Diagnosis

When making an initial diagnosis of ADPKD in an adult at risk, we recommend first using abdominal imaging by **ultrasound**.

Follow-up MRI or CT imaging may clarify the diagnosis and can provide prognostic information through MIC classification

# Ultrasound criteria for ADPKD Dx in people with a positive FH

| Ultrasound criteria by age group to diagnose ADPKD when there is a positive family history | | | | | | | |
|---|---|---|---|---|---|---|---|
| Age (years) | Number of cysts | PKD1 | | PKD2 | | Unknown gene type | |
| | | Predictive value of a negative test (%) | Sn (%) | Predictive value of a negative test (%) | Sn (%) | Predictive value of a negative test (%) | Sn (%) |
| 15–29 | ≥3 total | 100 | 94 | 100 | 70 | 100 | 82 |
| 30–39 | ≥3 total | 100 | 97 | 100 | 95 | 100 | 96 |
| 40–59 | ≥2 in each kidney | 100 | 93 | 100 | 89 | 100 | 90 |
| 60+ | ≥4 in each kidney | 100 | 100 | 100 | 100 | ND | ND |

# Ultrasound criteria for ADPKD exclusion in people with a positive FH

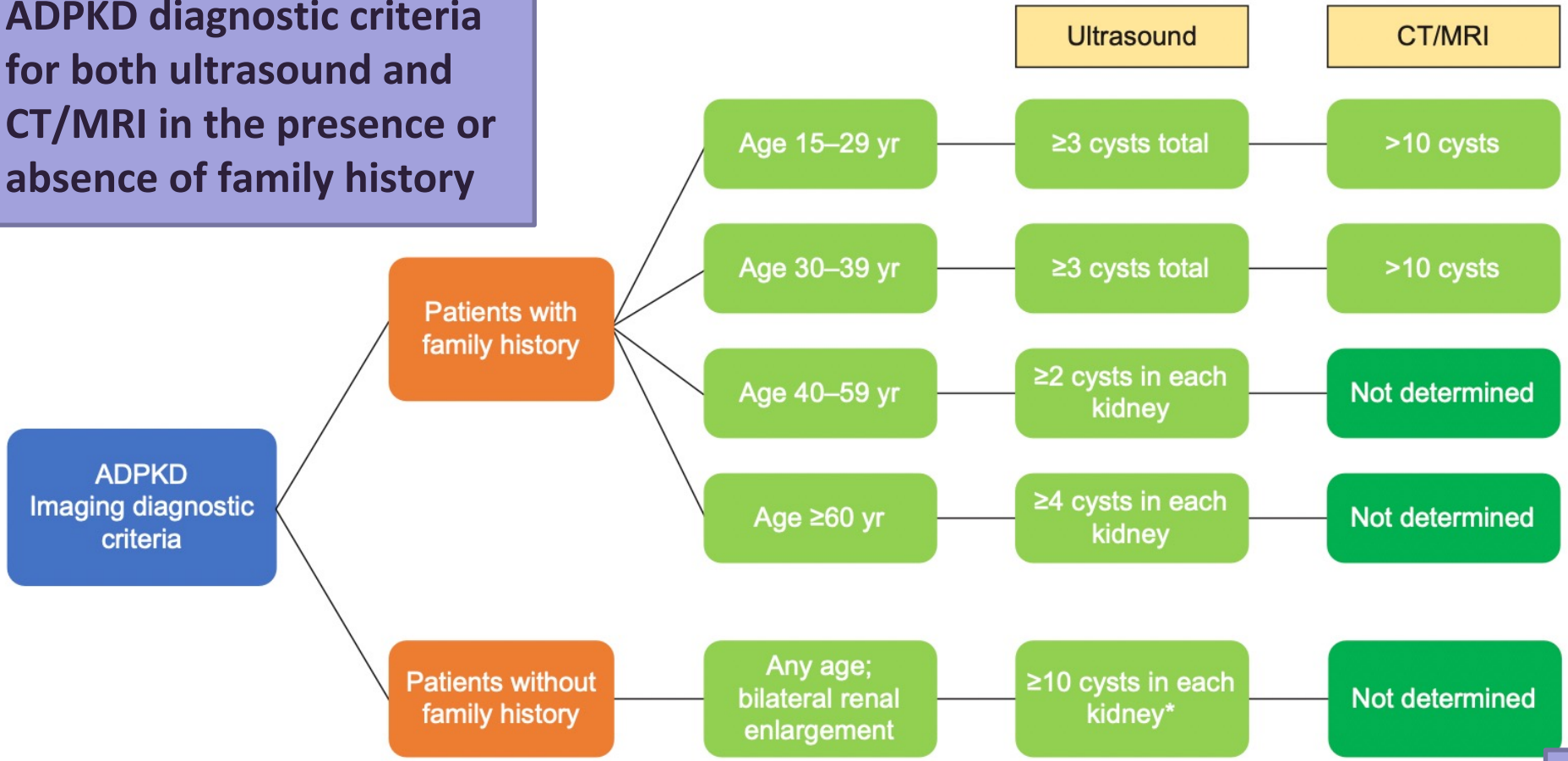
| Ultrasound criteria by age group to exclude ADPKD when there is a positive family history | | | | | | | |
|---|---|---|---|---|---|---|---|
| Age (years) | Test criterion (number of cysts) | PKD1 | | PKD2 | | Unknown gene type | |
| | | Predictive value of a negative test (%) | Sp (%) | Predictive value of a negative test (%) | Sp (%) | Predictive value of a negative test (%) | Sp (%) |
| 15–29 | ≥1 total | 99 | 98 | 84 | 97 | 91 | 97 |
| 30–39 | ≥1 total | 100 | 96 | 97 | 94 | 98 | 95 |
| 40–59 | ≥2 total | 100 | 98 | 100 | 98 | 100 | 98 |

# MRI criteria for ages 16-40 years in people with a positive FH

For people with a positive family history of ADPKD aged 16–40, the number of cysts seen on MRI have been described to diagnose or exclude ADPKD

| | |
|---|---|
| **>10 cysts total** | Sufficient for diagnosis (PPV and sensitivity = 100) |
| **<5 cysts total** | Sufficient for exclusion (NPV and specificity = 100) |

# ADPKD diagnostic criteria for both ultrasound and CT/MRI in the presence or absence of family history



# Diagnosis

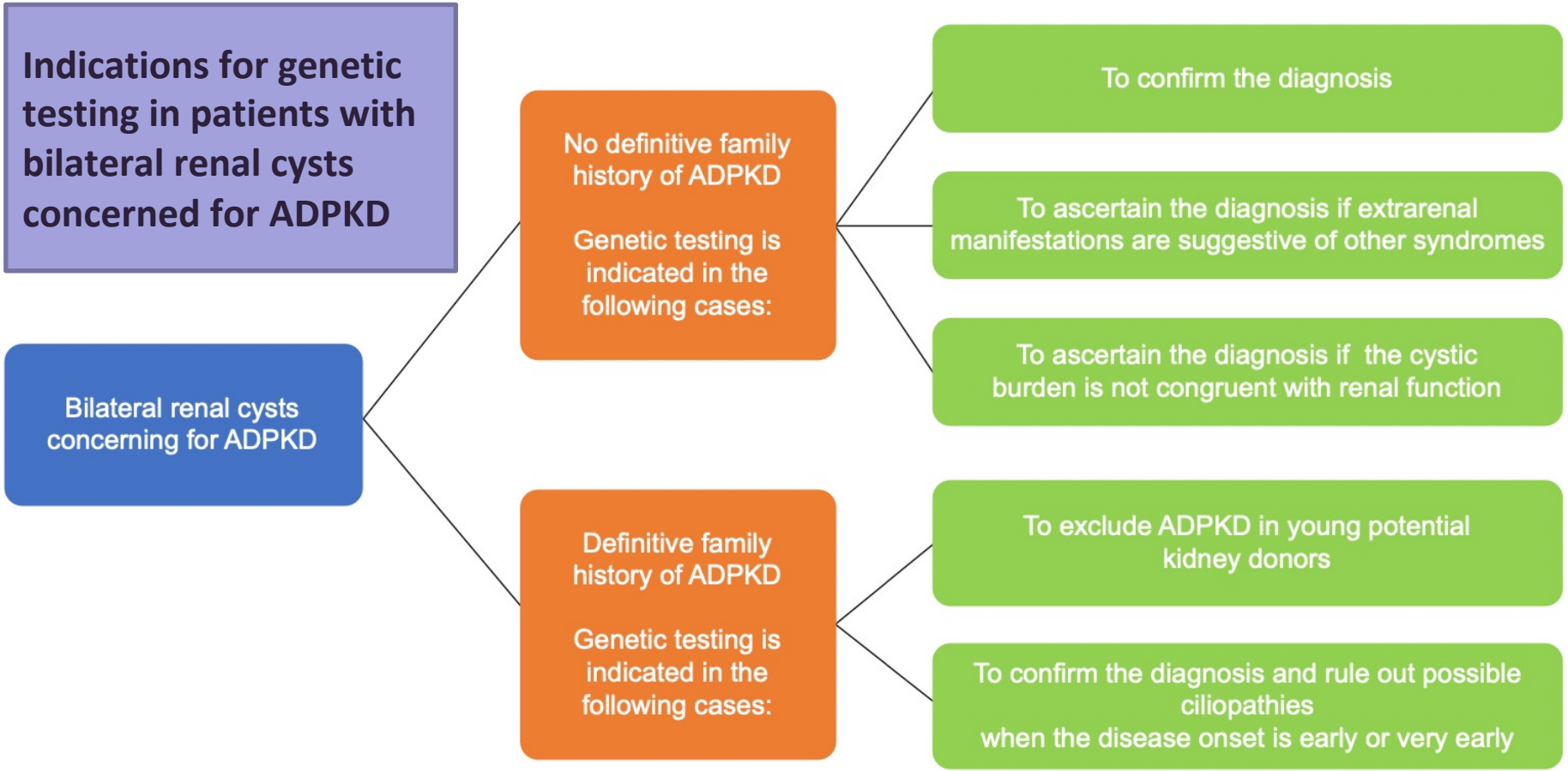
-For people with no known family history of ADPKD, kidney imaging plays an important role in the diagnosis of people with detected cysts.

-Genetic testing is **not required** to make an initial diagnosis of ADPKD in a person with a typical presentation

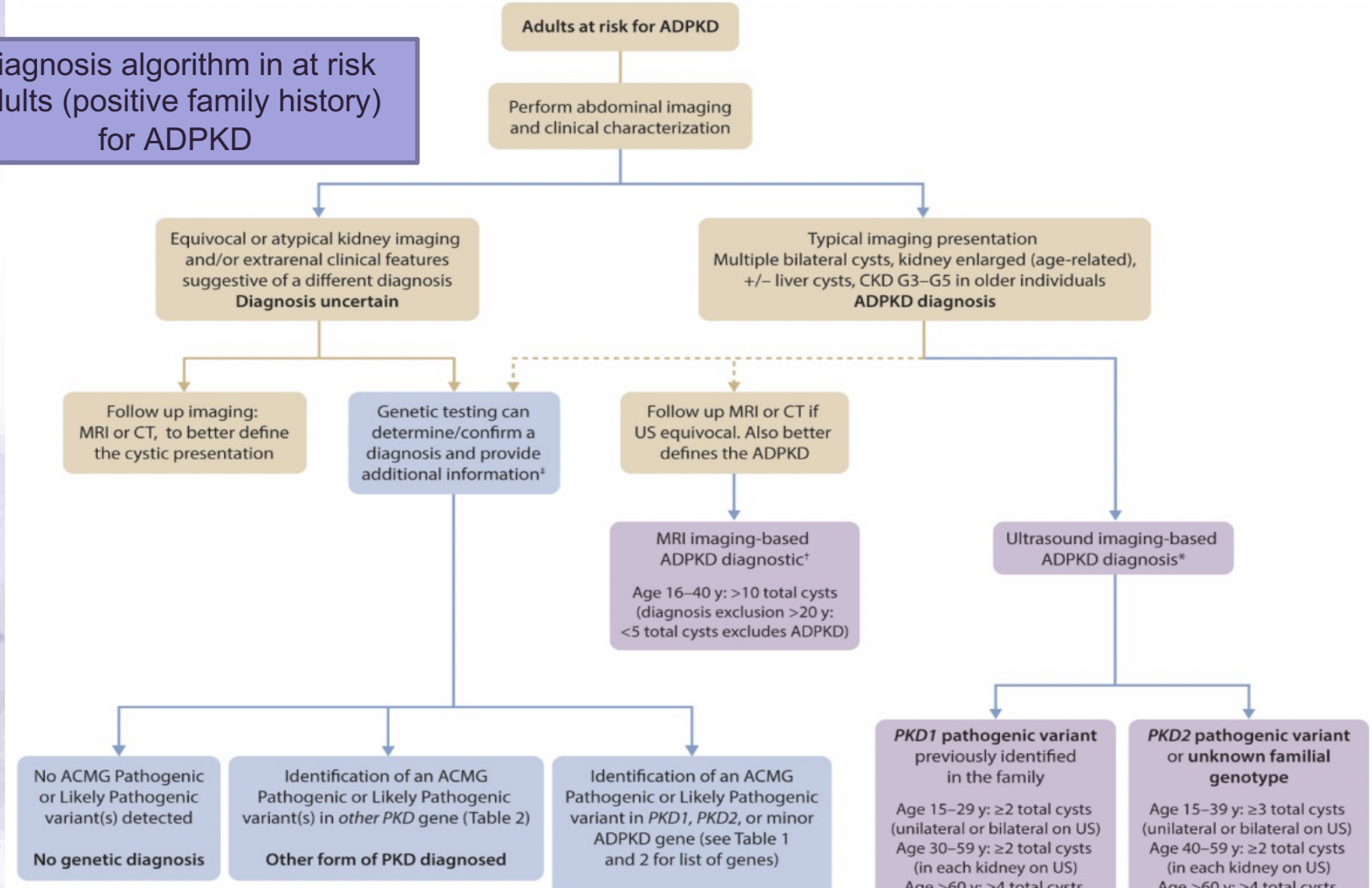
# Situations where genetic testing can clarify the diagnosis and aid prognosis

| | |
|---|---|
| Limited number of cysts | Negative family history |
| Variable disease severity in a family | Related living transplant donor ( |
| Atypical imaging, including asymmetric or unilateral disease | Family planning and PGD (preimplantation genetic diagnosis) |
| Discordance between structural (MIC) and functional (GFR) ADPKD severity* | VEO-ADPKD |

# Indications for genetic testing in patients with bilateral renal cysts concerned for ADPKD



# Diagnosis algorithm in at risk adults (positive family history) for ADPKD



# Diagnosis

A targeted next generation sequencing (tNGS) panel or other clinically accredited genetic or genomic test should be employed when performing genetic testing in people with ADPKD.

Genetic testing **is not always definitive** in a person with ADPKD caused by mutations in PKD1 or PKD2 because screening methods **do not detect all pathogenic variants.**

# Diagnosis

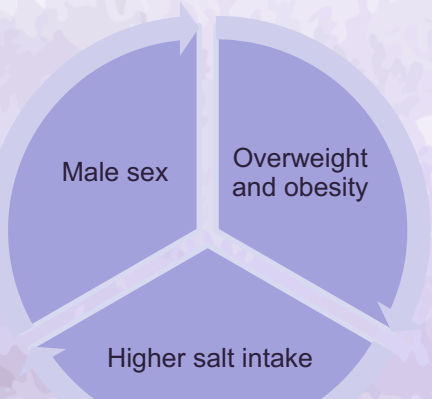
In a person with ADPKD and with a typical presentation, negative or uncertain genetic results do not exclude an inherited form of ADPKD

# Prognostics

The disease-causing gene influences the severity of kidney disease in ADPKD:

In PKD1: the type of PKD1 mutation.

The severity of kidney disease progression in the family: provides a rough guide to likely outcomes in other affected family members.



# Ways to assess the severity of kidney disease progression

Height-adjusted total kidney volume (htTKV) for prognostics is most accurately measured by MRI or CT scan, calculated using an automated tool or semiautomated tool.

Ultrasound-determined TKV and kidney length measurements also have prognostic value

**1** **Kidney Volume Calculator based on Ellipsoid equation (π/6xLxWxD) from MRI or CT image**

**Required Data Entry**

| **Right Kidney** | | **Left Kidney** | |
|---|---|---|---|
| Sagittal Length (mm) | | Sagittal Length (mm) | |
| Coronal Length (mm) | | Coronal Length (mm) | |
| Width (mm) | | Width (mm) | |
| Depth (mm) | | Depth (mm) | |

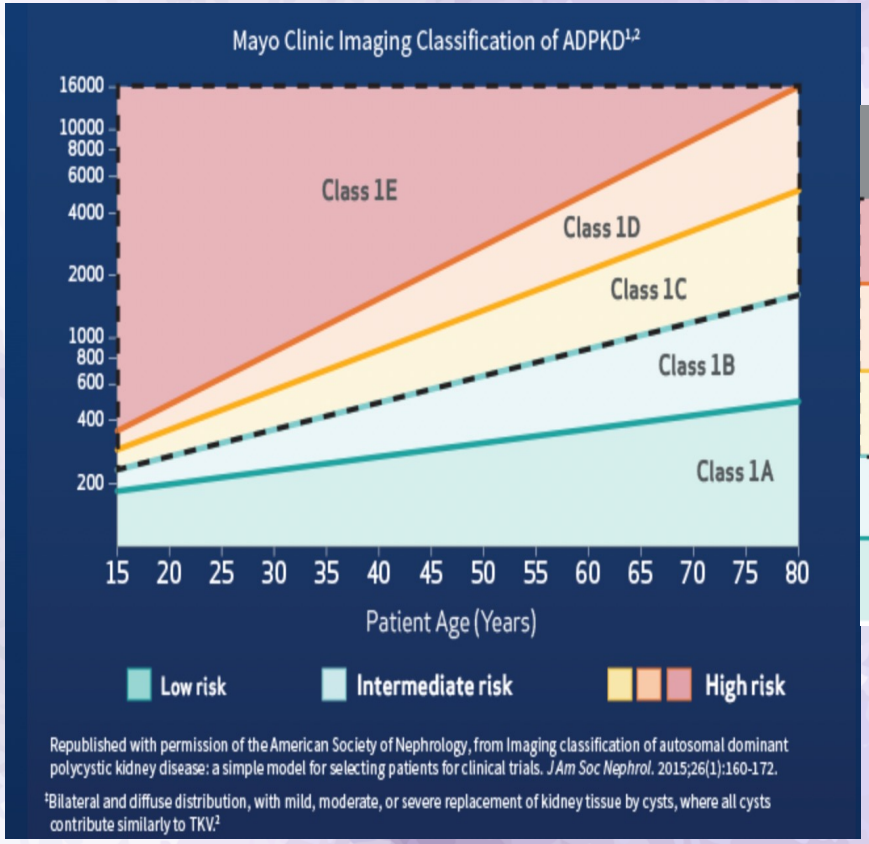
**Calculated Results**

**Right Kidney Volume (mL)** **Left Kidney Volume (mL)**

**Total Kidney Volume (mL)**

Clear All Calculate Volumes

# Height-adjusted total kidney volume

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[1]Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV.[2]

| Class | Est. kidney growth rate: yearly percentage increase | Estimated slope of change in eGFR | Risk for eGFR decline |
|---|---|---|---|
| 1E | >6.0% | -4.78 | High risk |
| 1D | 4.5% –6.0% | -3.48 | High risk |
| 1C | 3.0% – 4.5% | -2.63 | High risk |
| 1B | 1.5% – 3.0% | -1.33 | Intermediate risk |
| 1A | <1.5% | -0.23 | Low risk |

# The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score

Can aid the identification of people with rapidly progressive disease over 35 years of age

*J Am Soc Nephrol* 27: 942–951, 2016. doi: 10.1681/ASN.2015010016

## The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease

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# The Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score

| Variable | Points for PROPKD Score |
|---|---|
| Sex | |
| Female | 0 |
| Male | 1 |
| Hypertension before age 35 yr | |
| No | 0 |
| Yes | 2 |
| ≥1 urologic event before age 35 yr | |
| No | 0 |
| Yes | 2 |
| Mutation | |
| *PKD2* | 0 |
| *PKD1* nontruncating | 2 |
| *PKD1* truncating | 4 |

| Risk categories | point |
|---|---|
| Low risk | 0-3 |
| Intermediate risk | 4-6 |
| High risk | 7-9 |

Allows the possibility of ESRD onset before 60 years of age to be eliminated with a NPV of 81.4%

forecasts ESRD onset before 60 years of age with a PPV of 90.9%

# KIDNEY MANIFESTATIONS

## Hypertension

| Hypertension in ADPKD | | |
|---|---|---|
| **Monitoring** | **Non-pharmacologic interventions** | **Medical management** |
| • HBPM is preferred to office only measurements<br>• Consider ABPM in children, and in adults with difficult BP control, or LVH, proteinuria, or declining kidney function but normal office BP readings<br>• Consider work up for secondary high BP when >3 BP medications are needed in the setting of medication and dietary compliance | • Reduce dietary sodium including minimizing processed foods<br>• Optimize body weight with a healthy diet and regular exercise<br>• Optimize pain management, including sympathetic renal nerve inhibition, if appropriate | • Inhibition of RAS provides the cornerstone of BP management and includes the use of an ACEi or ARB<br>• Optimize BP control with addition of diuretic therapy to RAS blockade, if needed |

# Hypertension

-People with ADPKD aged 18–49 years with CKD **G1-G2** and BP >130/85 mm Hg, we recommend a target BP **≤110/75** mm Hg as measured by HBPM.
-People with **ADPKD ≥50 years** of age **and/or with** CKD G3-G5, we suggest a target mean SBP <120mmHg using office BP monitoring.

First line treatment: ACEIs or ARBs

# Hypertension

-We recommend avoiding any combination of ACEi, ARB, and DRI therapy in patients with ADPKD, with or without diabetes.

- Resistant high BP requiring ≥3 drugs should be investigated for causes of hypertension other than ADPKD

# Chronic kidney pain

-Nonpharmacological, noninvasive interventions should generally be considered as the initial treatment
Stepwise pharmacological treatment: when physical therapy does not adequately relieve pain.

# Chronic kidney pain

-Minimally invasive interventions: noninvasive management was ineffective and whose pain can be attributed to a single or to multiple dominant cysts.
-Celiac plexus block, isolated or followed by major splanchnic nerve block, and percutaneous renal denervation.
-Spinal cord stimulation: moderate-to-severe refractory mechanical or visceral pain.

# Chronic kidney pain

-Nephrectomy: reserved for **severe intractable chronic kidney pain** in selected people, typically with **advanced kidney disease** or after kidney failure, who have failed to respond to other modalities

# Other diseases

- **Nephrolithiasis**
- **Gout:**
  - For patients with first flare: against initiating ULT over no ULT.
  - For patients with first flare and CKD stage ≥3, serum **urate >9 mg/dl**, or **urolithiasis:** initiating ULT
  - In asymptomatic hyperuricemia (SU >6.8 mg/dl with no prior gout flares or subcutaneous tophi): against initiating drugs

# Gout

- Starting any ULT: **allopurinol** over all other ULT as the **preferred first-line agent** for all patients, including those with CKD stage ≥3.

- For allopurinol and febuxostat: starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., **≤100 mg/day** [and **lower in patients with CKD**] for allopurinol or ≤40 mg/day for febuxostat

# Gout

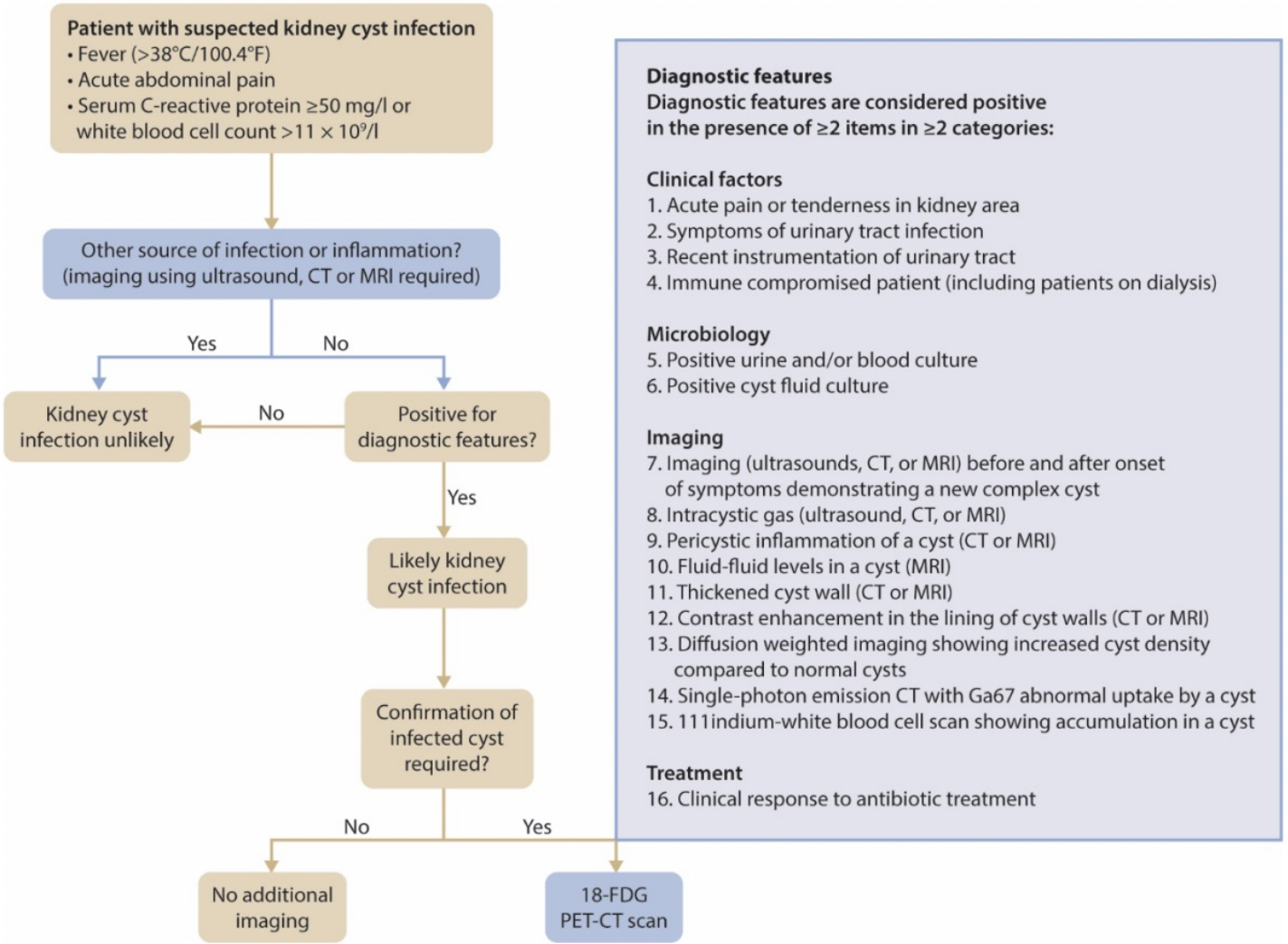
- ADPKD should not be treated for asymptomatic hyperuricemia.

- People with onset of hyperuricemia and gout in childhood or adolescence should be tested for autosomal dominant tubulointerstitial kidney disease (ADTKD).

# Other diseases

- **Hematuria:** should discuss the possibility of gross hematuria
- **Urinary tract infections**: should not treat **asymptomatic bacteriuria**
- **First-line therapy** (i.e., nitrofurantoin, TMP-SMX, fosfomycin): symptomatic UTIs in women
- Recurrent UTI patients experiencing acute cystitis episodes with as short a duration generally **no longer than seven days**

Diagnostic algorithm for infected kidney cyst



# Cyst infection

- ADPKD and kidney cyst infection: treatment with 4–6 weeks of antibiotic therapy rather than a shorter course.

- A lipid-soluble antibiotic (e.g., fluoroquinolones, trimethoprim-sulfamethoxazole) should be used to treat kidney cyst infection

# Renal cell carcinoma

- No clear association between ADPKD and an increased risk of RCC.
- Clinicians should be aware of atypical presentation of RCC in ADPKD

# CKD MANAGEMENT AND PROGRESSION, KIDNEY FAILURE, AND KIDNEY REPLACEMENT THERAPY

# CKD management and progression

- Avoid transfusions.
- Hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI) should not routinely be used to manage anemia in people with ADPKD
- DM with ADPKD should be the same as for people with other forms of CKD, with the **possible exception** that SGLT2i **are not** recommended at this time to be used to manage diabetes in people with ADPKD.

# Kidney transplantation

- A kidney transplant from a living donor provides lower risk of rejection and longer allograft survival
- Preemptive living donor kidney transplantation is the optimal therapy for people with ADPKD

Nephrectomy in kidney transplant candidate

| |
|---|
| Recurrent and/or severe kidney infection |
| Symptomatic nephrolithiasis |
| Recurrent and/or severe kidney cyst bleeding |
| Intractable pain |
| Suspicion of kidney cancer |
| Insufficient space for insertion of a kidney graft |
| Ventral hernia in the setting of massively enlarged kidneys |
| Severe symptoms related to massively enlarged kidneys* |

# Kidney transplantation

- **unilateral** rather than bilateral native kidney nephrectomy in people with ADPKD
- When? **at the time of or after**, but not before, transplantation, whenever possible.
- Evaluation for RCC in pretransplant people with ADPKD : imaging of the kidneys (e.g., abdominal **MRI**) **within 1 year** prior to transplantation should be considered.

# THERAPIES TO DELAY THE PROGRESSION OF KIDNEY DISEASE

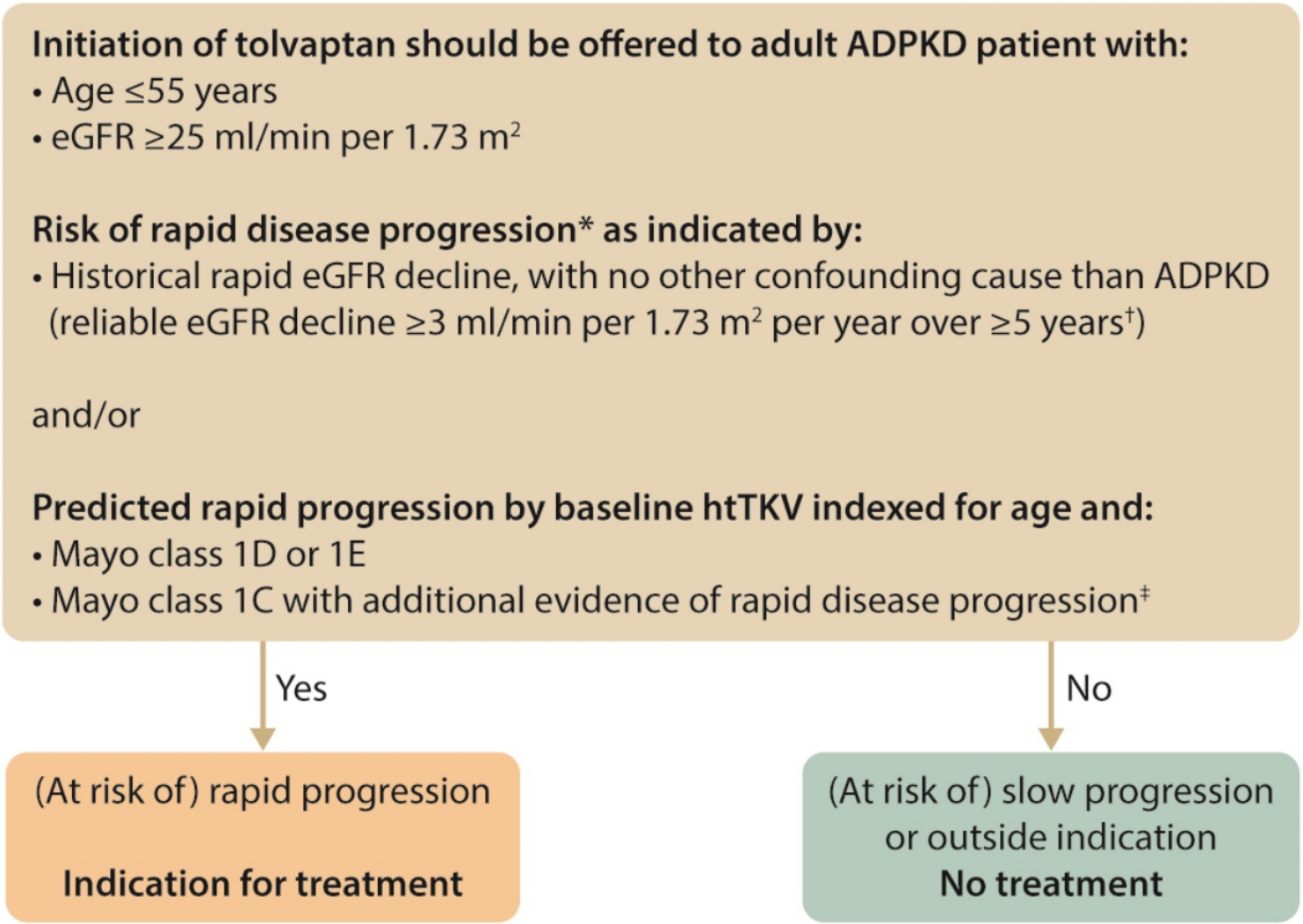
# Tolvaptan

- Indications for tolvaptan in ADPKD:
- ADPKD aged 18-55 years with eGFR ≥25 ml/min/1.73 m2 who have or are at risk for rapidly progressive disease.

# Rapid disease progression:

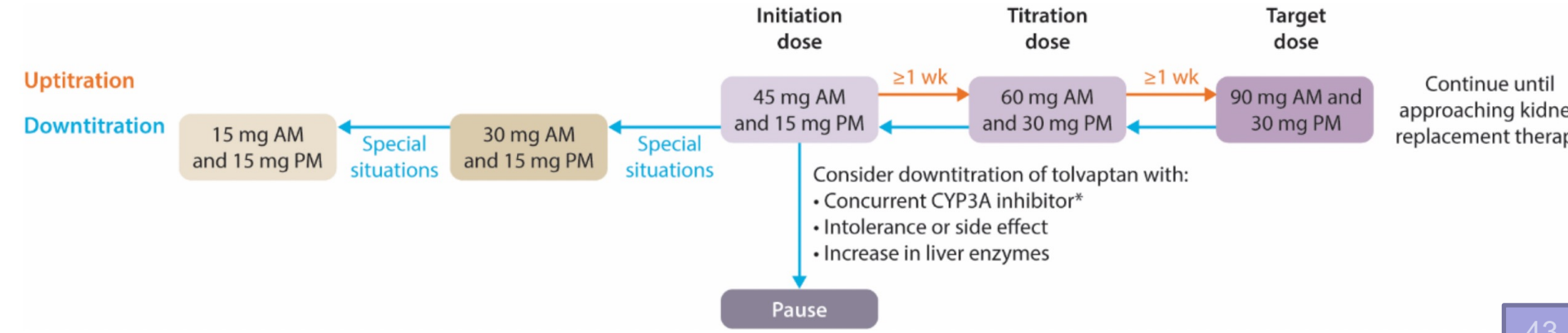
- A confirmed annual eGFR decline ≥3 ml/min per 1.73 m2 , based on ≥5 measurements over a period of ≥5 years
- A person with ADPKD has CKD G3-G5 < 45 years
- Enlarged kidneys
- No other explanation for reduced kidney function

KDIGO algorithm to decide to whom to prescribe tolvaptan

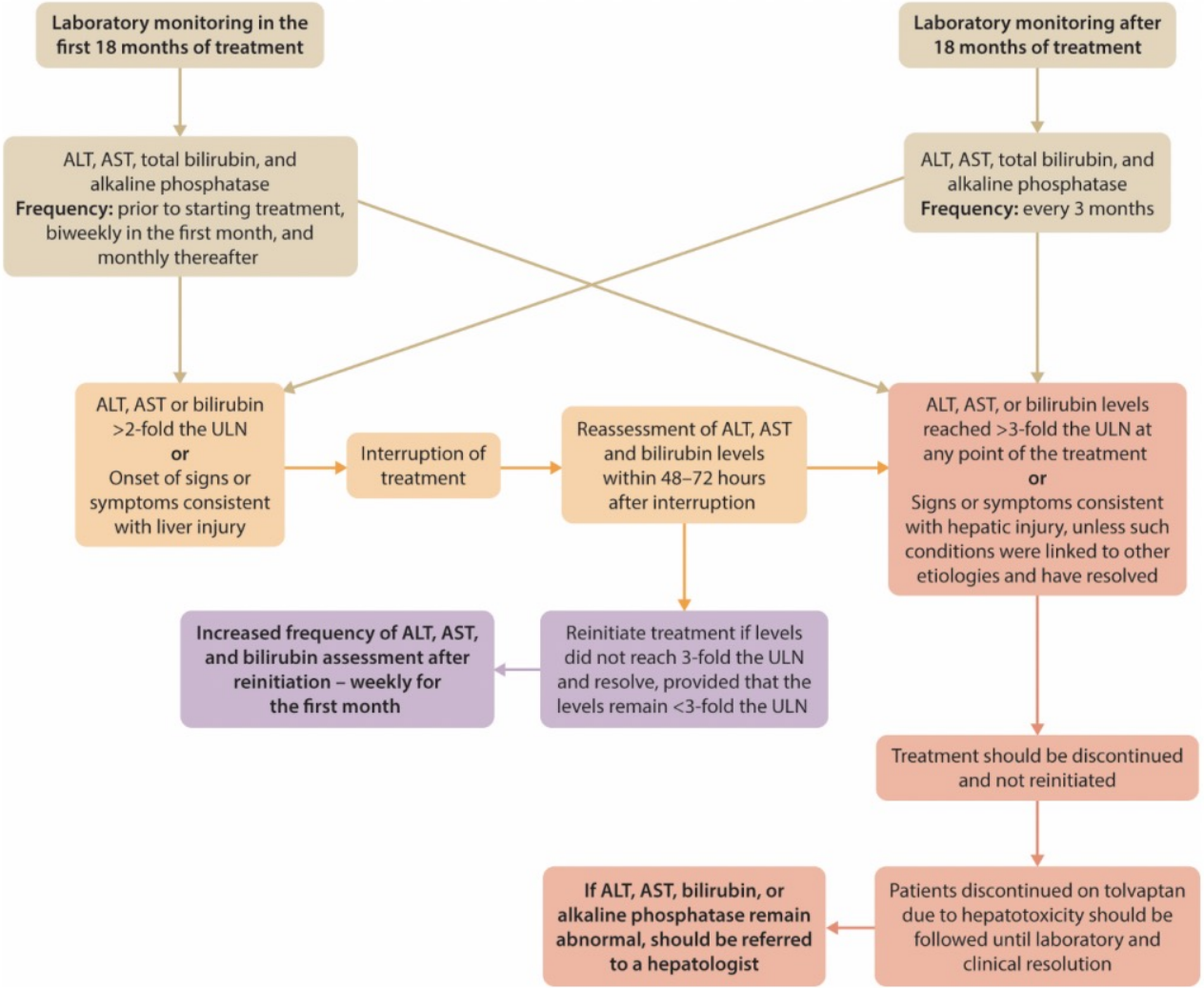


# Tolvaptan therapy

- Primary imaging method for risk prediction: MRI



Monitoring and management for potential hepatotoxicity in people with ADPKD on chronic treatment with tolvaptan.



# Tolvaptan therapy

- Should be instructed to respond to thirst.
- Maintained until : approach the need of KRT initiation. Discontinuation may slightly increase eGFR

# Water intake in the absence of tolvaptan

- Achieve at least 2 liters of urine per day in ADPKD and an eGFR ≥30 ml/min per 1.73 m2 without contraindications to excreting a solute load

# Other drugs to slow kidney disease progression

- Not using mTOR inhibitors
- Not using statins
- Not using metformin
- Should not be used  SGLT2 inhibitors

# Other drugs to slow kidney disease progression

- Somatostatin analogues should be prescribed only in people with ADPKD with **severe symptoms** due to massively enlarged kidneys or in ADPLD
- **Not be** prescribed for the sole purpose of **improving the rate of eGFR loss** in people with ADPKD.

# INTRACRANIAL ANEURYSMS (ICA)

| | General population | General population plus family history of ICA or SAH | ADPKD population | ADPKD population plus family history of ICA or SAH |
|---|---|---|---|---|
| **Prevalence of ICA** (95% CI) | 3.2% (1.9–5.2) | 4% (2.6–5.8)[a]<br>11% (9–14)[b] | 12.9% (10.4-15.4) (Figure 36) | 18% (13–24)[c]<br>22% (14–31)[d] |
| **Incidence rates of SAH** (per 1000 person-years, 95% CI) | 0.079 (0.069–0.09)[e] | 3–7 higher risk | 0.57 (0.19-1.14) (Figure 37) | Likely higher (based on data from general population) |

# Screening for ICA:

- A personal history of SAH o
- Positive FH of ICA, SAH
- Unexplained sudden death if the person will be eligible for treatment and has reasonable life expectancy.
- De novo ADPKD
- Unknown FH or small number of ADPKD-affected relatives
- Personal or FH of extracerebral vascular phenotype
- Evaluation for kidney and/or liver transplantation or before **major** elective surgery

# Take home messages

- Clinical and imaging finding of ADPKD is sufficient for diagnosis
- Genetic evaluation in some specific situations
- Management of related diseases is necessary: HTN, Gout, chronic pain, ….
- Treatment options: tolvaptan and water intake

# References

KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE EVALUATION, MANAGEMENT, AND TREATMENT OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

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KIDNEY RESEARCH AND CLINICAL PRACTICE

## Management of autosomal dominant polycystic kidney disease in the era of disease-modifying treatment options

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