
# Πολυκυστική νόσος των νεφρών: οι νέες κατευθυντήριες οδηγίες

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

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**PUBLIC REVIEW DRAFT**
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# ΟΝΟΜΑΤΟΛΟΓΙΑ ADPKD

**Practice Point 1.1.1:** In genetically defined people with autosomal dominant polycystic kidney disease (ADPKD), a common nomenclature should include the disease name followed by the gene name. Πχ **ADPKD-PKD1**

**Practice Point 1.1.2:** People who have an ADPKD or autosomal dominant polycystic liver disease (ADPLD) spectrum phenotype but have not been genetically screened will continue to be termed **ADPKD** or ADPLD.

**Practice Point 1.1.3:** 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.

**Practice Point 1.1.4:** For people who are genetically screened, ADPKD will be employed as the name of the disease resulting from mutation to the major ADPKD genes, PKD1 or PKD2, and the minor ADPKD loci. Πχ **ADPKD-DNAJB11**

| Gene | % screened families | # of families * | Disease designation | Kidney phenotype | Extrarenal phenotype | Comments |
|---|---|---|---|---|---|---|
| Unknown/not screened | | | ADPKD | Bilateral PKD, kidney enlargement, age-related CKD, may result in KF | Liver cysts, including severe PLD, increased risk of ICA | A wide phenotypic range in terms of TKV and KF risk and timing |
| ***PKD1*** | ~48% | >3250 | Truncating pathogenic variant: ADPKD-*PKD1* | Bilateral PKD, early kidney enlargement, CKD G3, ~ 40 y, KF in 50s | Liver cysts, including severe PLD, increased risk of ICA | Includes some disease variability including a more benign course, sometimes associated with mosaicism |
| | ~19% | >1750 | Nontruncating pathogenic variant: ADPKD-*PKD1* | Bilateral PKD, kidney enlargement, age-related CKD, may result in KF | Liver cysts, including severe PLD, increased risk of ICA | Phenotype ranges from severe as *PKD1* truncating to mild PKD in old age, partly depending on the degree of residual protein function |
| ***PKD2*** | ~15% | >1000 | ADPKD-*PKD2* | Bilateral PKD, milder and later kidney enlargement, CKD G3, ~55 y, KF in 70s | Liver cysts, including severe PLD, increased risk of ICA | Includes some disease variability including a more severe or more benign course |
| *ALG5* | <0.5% | <10 | ADPKD-*ALG5* | Mild to moderate cyst development with limited kidney enlargement and fibrosis CKD and some KF in older subjects | A few liver cysts in a minority of people | |
| *ALG6* | <0.5% | <10 | ADPKD-*ALG6* | Generally mild with or without preserved kidney function | Liver cysts including severe PLD | Can present as ADPLD.[4] |
| *ALG8* | ~1% | <40[†] | ADPKD-*ALG8* | Generally mild cystic kidney disease with preserved function into old age | Liver cysts, including severe PLD. ICA risk unclear | Can present as ADPLD. *ALG8* is likely a low penetrant genotype.[4,8] |
| *ALG9* | <0.5% | <20 | ADPKD-*ALG9* | Mild to moderate cystic disease with significant CKD in older people | Liver cysts are common | |
| *DNAJB11* | <0.5% | <30 | ADPKD-*DNAJB11* | Bilateral small cysts, limited or no kidney enlargement, progressive fibrosis, limited CKD G3a <55 y, but KF in 70s | Liver cysts, usually mild, ICA and vascular risk is possible | ADPKD-*DNAJB11* has similarities to ADTKD, because of the small, fibrotic kidneys, but visible cysts are usually present |
| *GANAB* | <0.5% | <20 | ADPKD-*GANAB* | Mild cyst development, limited CKD, no KF | Liver cysts, including severe PLD. ICA risk unclear | Can present as ADPLD |
| *IFT140* | 1%–2% | <50 | ADPKD-*IFT140* | Few, large bilateral cysts resulting in kidney enlargement, with kidney function usually preserved into old age | Liver cysts only rarely seen, with risk of ICA unclear | |
| *NEK8*[¶] | <0.5% | <20 | ADPKD-*NEK8* | Bilateral PKD, kidney enlargement, KF in childhood, occasionally later in cases of specific alleles and mosaicism | Liver cysts rare | De novo occurrence was reported in 75% of the published cases.[9] |
| *PKHD1* | ~1% | <50[†] | ADPKD-*PKHD1* | Generally, very mild cystic kidney development with preserved function into old age | Liver cysts are common, and can be see without kidney cysts | Biallelic pathogenic variants are associated with ARPKD. Can present as ADPLD. Monoallelic PKHD1 is likely a low penetrant genotype.[5] |
| Genetically unresolved by testing | ~5% | | ADPKD | Typically, mild cyst development with limited CKD and KF | Liver cysts | Most unresolved cases have relatively mild disease |

**Practice Point 1.1.5:** For people who are genetically screened, ADPLD will be employed as the disease name for the **major ADPLD genes**, **PRKCSH or SEC63**, and the minor ADPLD loci.

| Gene | % screened families | # of families * | Disease designation | Liver phenotype | Kidney phenotype | Comments |
|---|---|---|---|---|---|---|
| Not screened | | | ADPLD | Multiple liver cysts and often liver enlargement | None, or very few kidney cysts | Disease is highly variable from few liver cysts to massive PLD |
| ***PRKCSH*** | ~20% | >40 | ADPLD-*PRKCSH* | Multiple liver cysts and often liver enlargement | None, or very few kidney cysts | Disease is highly variable from few liver cysts to massive PLD |
| ***SEC63*** | ~15% | >40 | ADPLD-*SEC63* | Multiple liver cysts and often liver enlargement | None, or very few kidney cysts | Disease is highly variable from few liver cysts to massive PLD |
| *ALG6* | <1% | <10 | ADPLD-*ALG6* | Liver cysts including severe PLD | Kidney cyst number variable from none to multiple | Can present as ADPKD.‡ |
| *ALG8* | 5–10% | <20† | ADPLD-*ALG8* | Multiple liver cysts and often liver enlargement, but liver cysts may not be present | Kidney cyst number variable from none to multiple, including an ADPKD spectrum phenotype | Can present as ADPKD-*ALG8*. *ALG8* is likely a lower penetrant phenotype |
| *GANAB* | 1–5% | <10 | ADPKD-*GANAB* | Multiple liver cysts and often liver enlargement, but liver cysts may not be present | Kidney cyst number variable from none to multiple, including an ADPKD spectrum phenotype | Can present as ADPKD-*GANAB* |
| *LRP5* | <1% | 4 | ADPKD-*LRP5* | Multiple liver cysts and often liver enlargement | None, or very few kidney cysts | Based on missense variants in 1 family and 3 people. Monoallelic *LRP5* variants are also associated with familial exudative vitreoretinopathy |
| *PKHD1* | ~1% | <25† | ADPLD-*PKHD1* | Generally, very mild cystic kidney development with preserved function into old age | Liver cysts are common and can be seen without kidney cysts. Not usually associated with severe PLD | Biallelic pathogenic variants are associated with ARPKD. Can present as ADPKD-*PKHD1* |
| *SEC61B* | <1% | 2 | ADPLD-*SEC61B* | Numerous small cysts | Very few or none | Data based on 2 people |
| Genetically unresolved | ~50% | | ADPLD | Multiple liver cysts but tendency for milder PLD | None, or very few kidney cysts | Disease is highly variable from few liver cysts to massive PLD |

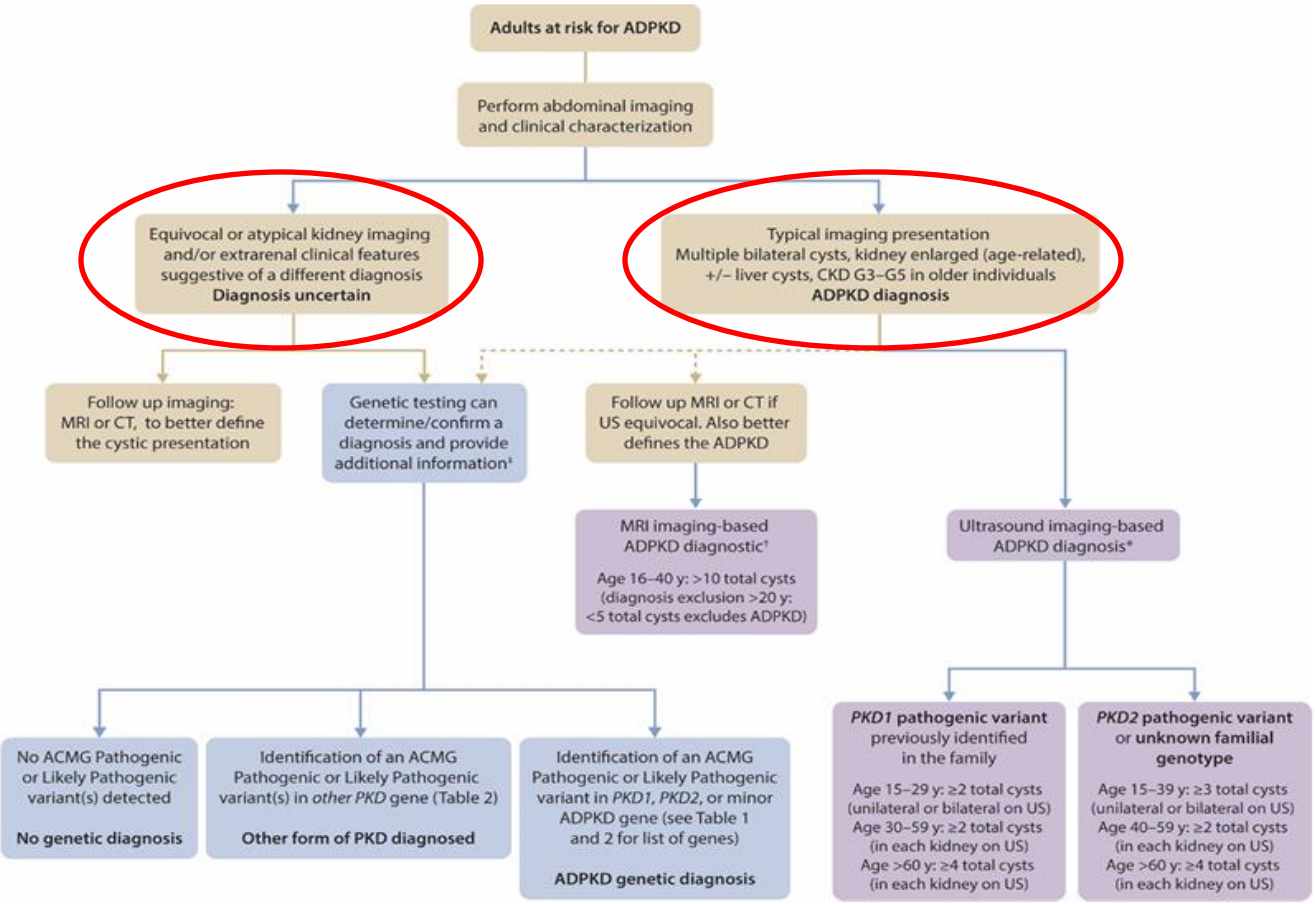
**Practice Point 1.1.6:** Designation of **PKD1 pathogenic variants** as **truncating** (T) or **nontruncating** (NT) should be noted, but not incorporated into the nomenclature.

# ΔΙΑΓΝΩΣΗ ADPKD

**Recommendation 1.3.1:** When making an initial diagnosis of ADPKD in an adult at risk, we recommend **first using abdominal imaging by ultrasound**. Follow-up magnetic resonance imaging (MRI) or computed tomography (CT) imaging may clarify the diagnosis and can provide prognostic information through MIC classification (1B).

Η **διάγνωση με υπέρηχο ή με MRI ισχύει μόνο για τυπική ΠΚΝ**, δηλαδή τυπική απεικονιστική εικόνα με πολλαπλές κύστεις άμφω, μεγάλο μέγεθος νεφρών σε σχέση με την ηλικία, με ή χωρίς ηπατικές κύστεις, ΧΝΝ 3-5 σε άτομα μεγαλύτερης ηλικίας

# Διαγνωστικός αλγόριθμος σε άτομα με θετικό οικογενειακό ιστορικό



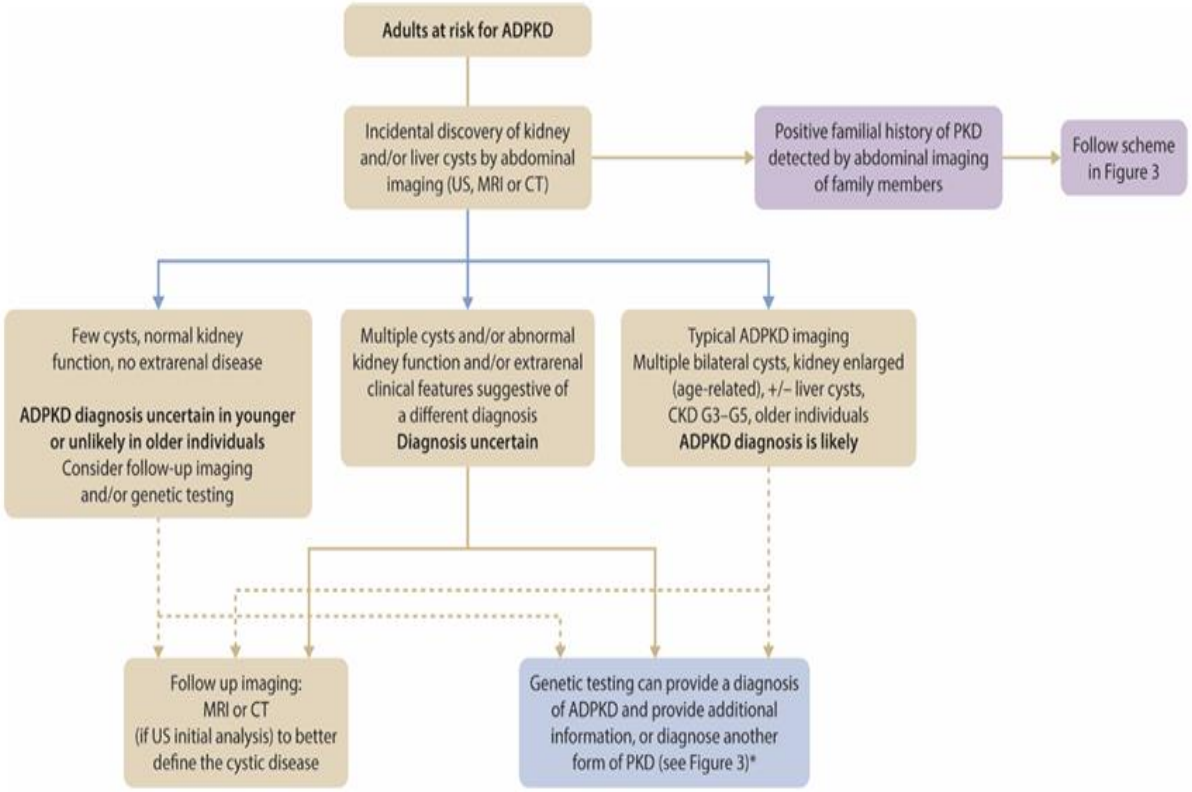
# Διάγνωση και αποκλεισμός της νόσου με MRI

**Practice Point 1.3.4:** 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) |

***Figure 7. Magnetic resonance imaging (MRI) criteria for ages 16-40 years in people with a positive family history.***[25] NPV, negative predictive value; PPV, positive predictive value.

# Διαγνωστικός αλγόριθμος σε άτομα όπου νεφρικές ή/και ηπατικές κύστεις ανιχνεύονται τυχαία (αρνητικό ή ασαφές οικογενειακό ιστορικό)



| Possible benefits of early screening | Possible harms of early screening |
|---|---|
| • **Resolve diagnosis odyssey.** The individual person and family may obtain a definite diagnosis.<br>• **Ability to manage and treat ADPKD.** Appropriate management and treatment of the affected person can be initiated.<br>• **Initiate screening for extrarenal manifestations**.<br>• **Enable enrollment in clinical trials.**<br>• **Reassurance of unaffected people**. Negative imaging and/or genetic testing results in at-risk family members will likely provide relief to the person and may influence family-planning decisions.<br>• **Appropriate family planning**. Knowledge about the genetic nature of ADPKD might aid decision-making concerning care of the person and family planning.<br>• **Appropriate selection of unaffected relatives as possible donors for kidney transplantation**. Negative imaging and/or genetic results can identify suitable living related donors.<br>• **Facilitate testing of family members**. A positive genetic test allows inexpensive screening of other interested at-risk family members, allowing appropriate management of those affected.<br>• **Implement lifestyle modifications**. Details in Chapter 7. | • **Psychologic burden of having a life-altering diagnosis.** Obtaining a diagnosis of ADPKD may lead to a range of emotions (e.g., anxiety about the future, anger, guilt about transmission to offspring).<br>• **Possible difficulties with employment and insurability** Despite legislation in many countries, the diagnosis of a genetic disease can have certain insurance (e.g., life, health, disability) and workplace implications. However, it is important to consider that being at risk of ADPKD, without a firm diagnosis, may also have insurability implications.<br>• **High cost.** Some testing, including genetic testing and certain types of imaging, may not be fully covered by insurance or government funded health plans.<br>• **Imaging and/or genetic testing results may be inconclusive.** In >25% of cases genetic testing does not result in a certain diagnosis, and imaging can provide equivocal results. Both may lead to false reassurance and erroneous decision-making.<br>• **Specialist knowledge to interpret test results may not always be available**. Supply of professionals with genetics expertise for kidney diseases is limited. |

**Table 2.** Situations where genetic testing can clarify the diagnosis and aid prognosis.

| Situation | Genetic findings |
|---|---|
| Limited number of cysts | Positive result can show a genetic origin (minor gene or hypomorphic allele) |
| Variable disease severity in a family | Mosaicism or biallelic/digenic disease can explain some extreme variability |
| Atypical imaging, including asymmetric or unilateral disease | Positive result can show a genetic origin (mosaicism or minor gene involvement) |
| Discordance between structural (MIC) and functional (GFR) ADPKD severity* | Genetic testing may reveal an atypical form of the disease or additional genetic or contributory factors. Non-genetic factors may also be important. |
| Negative family history | Positive result can show a genetic origin (*de novo* mutation can be proven) |
| VEO-ADPKD | Biallelic disease may be found (Chapter 9) |
| Related living transplant donor (<30 years and/or a few cysts detected) | Genetic testing can exclude the familial variant and test for other genetic causes |
| Family planning and PGD | Obtaining a genetic diagnosis can aid family planning and enable PGD (Chapter 8) |
| All people | Genetics can confirm the diagnosis, identify the responsible gene and variant, and provide prognostic information |

# Περιπτώσεις στις οποίες ο γενετικός έλεγχος έχει θέση για διαλεύκανση της διάγνωσης ή για προγνωστικούς λόγους

Σε **άτυπες περιπτώσεις**, όπως πρώιμη και ιδιαίτερα σοβαρή νόσο (VEO, very early onset), ή ιδιαίτερα ήπια νόσο (υπομορφικά αλλήλια, μωσαϊκισμος), όταν η βαρύτητα της νόσου ποικίλει μέσα στην ίδια οικογένεια (Mosaicism or biallelic/digenic disease), σε περίπτωση που ο απεικονιστικός έλεγχος εμφανίζει ασυμμετρία ως προς το μέγεθος των νεφρών ή κύστεις μόνο στον ένα νεφρό

**Ασυμφωνία** μεταξύ της απεικονιστικής/δομικής ταξινόμησης/βαρύτητας (MIC) και της βαρύτητας στην έκπτωση της νεφρικής λειτουργίας (GFR)

**Αρνητικό οικογενειακό ιστορικό** (ο έλεγχος μπορεί να αποκαλύψει κάποια de novo μετάλλαξη)

Σε νεαρά άτομα (<30) με οικογενειακό ιστορικό ADPKD, που είναι **υποψήφιοι συγγενείς δότες νεφρού** εφόσον ο απεικονιστικός έλεγχος είναι αμφίβολος ή αρνητικός ή σε περίπτωση υποψήφιου δότη στον οποία ανιχνεύονται κάποιες κύστεις χωρίς γνωστό οικογενειακό ιστορικό

Για **οικογενειακό προγραμματισμό** ή και **προεμφυτευτική γενετική διάγνωση**

Η γενετική διάγνωση μπορεί να είναι **χρήσιμη σε όλους** για την επιβεβαίωση της διάγνωσης και για προγνωστικούς λόγους

**Genetic testing methods for screening** for autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (ADPLD)

- **Targeted next generation sequencing (tNGS) gene panel (PKD & ciliopathy genes ~ 150, nephrology genes ~ 600)**
- Sanger sequencing
- Whole exome sequencing (WES) slice
- Whole genome sequencing (WGS) slice

**Currently, a PKD/Nephrology tNGS panel is the most effective and cost-effective means to genetically screen people with suspected ADPKD**

**Sanger sequencing of single or small number of genes is discouraged**

Practice Point 1.3.13: **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 and some variants are not classed as pathogenic using ACMG guidelines.**

Practice Point 1.3.16: In a family with a known gene variant, **screening for the specific variant (Sanger sequencing, στοχευμένος γενετικός έλεγχος)** is usually sufficient to diagnose or exclude ADPKD or to determine affected status.

Practice Point 1.3.14: **In a person with ADPKD and with a typical presentation, negative or uncertain genetic results do not exclude an inherited form of ADPKD.**

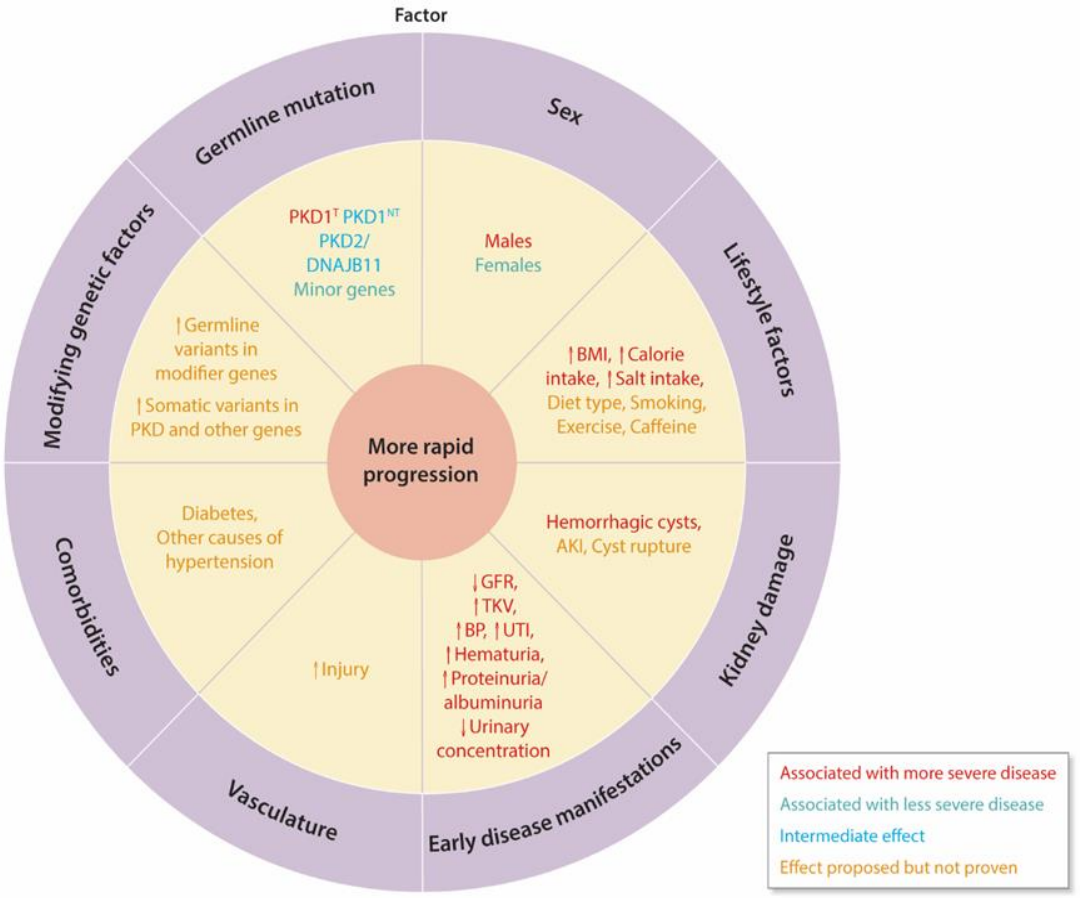
- **Pathogenic** (P) or **Likely Pathogenic** (LP) variant is detected in a known ADPKD gene → A genetic diagnosis of ADPKD is made.
- One or more **variant of uncertain significance (VUS)** is detected in a known ADPKD gene → A genetic diagnosis of ADPKD is not made but clinical diagnosis should be sufficient to start treatment or enroll in a clinical trial. Family segregation of VUS may allow reclassification to LP or Likely Benign (LB). If negative F/H, testing of parents may confirm a *de novo* variant; allow the VUS to be reclassified as LP.
- **No significant variants** are detected → A genetic diagnosis of ADPKD is not made but clinical diagnosis should be sufficient to start treatment or enroll in a clinical trial. Consider rescreening of PKD1 by Sanger analysis or WGS. If negative F/H, screen for mosaicism. P/LP variants, especially in PKD1 may be missed by present screening methods.

Practice Point 1.3.15: **In a person with ADPKD and atypical imaging or another unusual presentation, negative or uncertain genetic results do not exclude an inherited form of PKD.**

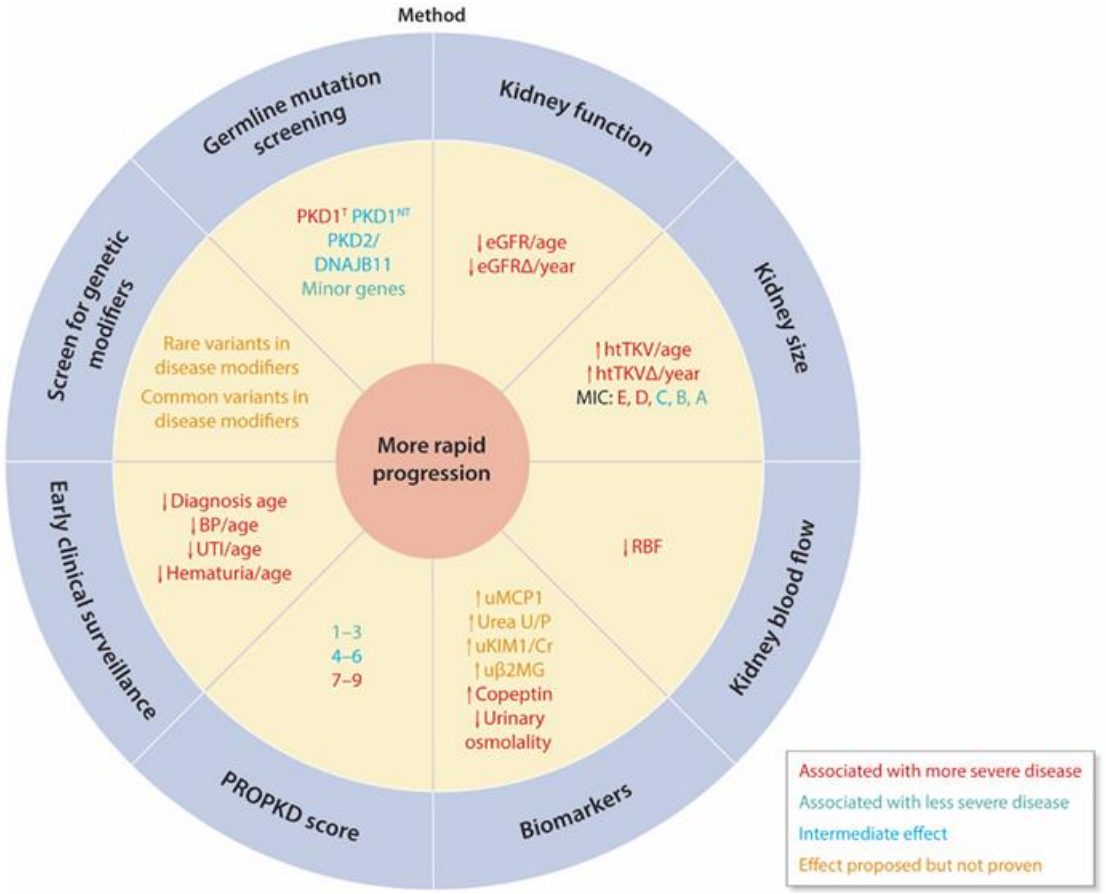
- **P or LP variant is detected in a known ADPKD gene** → A genetic diagnosis of ADPKD is made.
- One or more **VUS** is detected in a known ADPKD gene → A genetic diagnosis of ADPKD is not made
  PKD without kidney enlargement may limit treatment options and enrollment in clinical trials
  Family segregation of VUS may allow reclassification to LP or LB.
  If negative F/H, testing of parents may confirm a de novo variant; allow the VUS to be reclassified as LP
- **No significant variants** are detected → A genetic diagnosis of ADPKD is not made
  The mild PKD may limit treatment options and enrollment in clinical trials
  Consider rescreening of PKD1 by Sanger analysis or WGS.
  If negative F/H, screen for mosaicism. P/LP variants, especially in PKD1 may be missed by present screening methods.
- A **P/LP variant is found in another dominantly inherited PKD-related gene** → A genetic diagnosis of the implicated disorder is made.

# 1.4. **Prognostics**

## 1.4.1. Factors associated with the severity of kidney disease in ADPKD

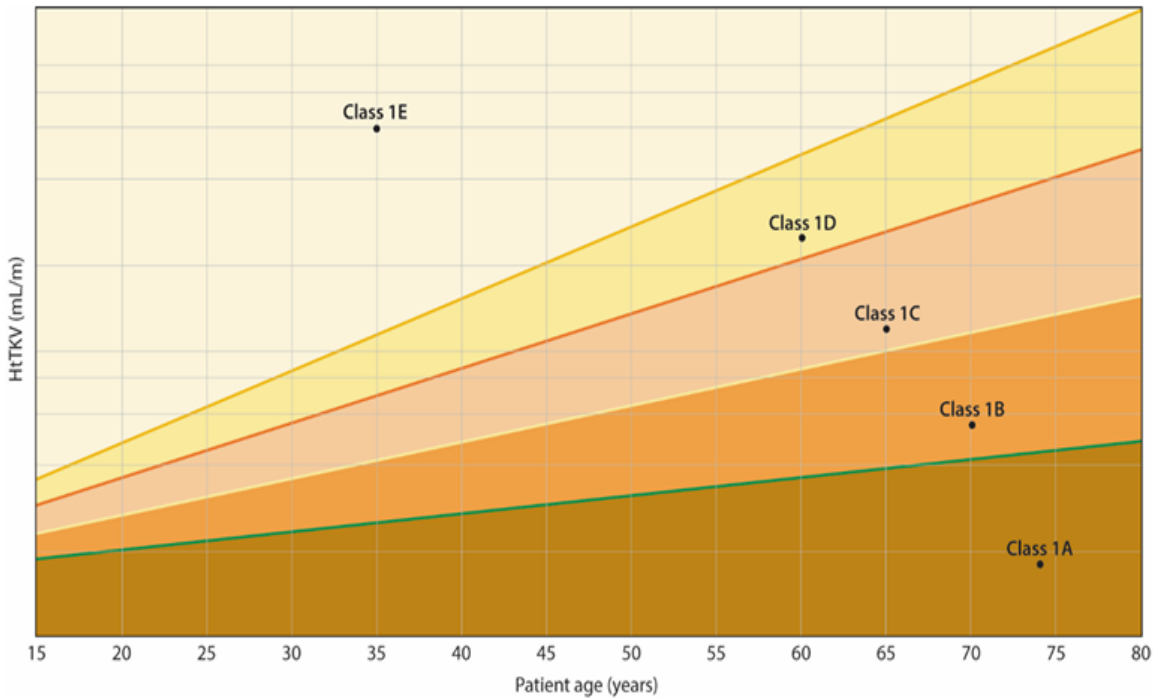


# 1.4.2. **Ways to assess the severity of kidney disease progression**



Recommendation 1.4.2.1: **We recommend employing the Mayo Imaging Class (MIC) to predict future decline in kidney function and the timing of kidney failure (1B).**

| Class, subclass, and term | Description |
|---|---|
| 1. Typical ADPKD | Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV |
| 2. Atypical ADPKD | |
| A | |
| Unilateral | Diffuse cystic involvement of one kidney causing marked renal enlargement with a normal contralateral kidney defined by a normal kidney volume (<275 ml in men; <244 ml in women) and having no or only 1–2 cysts |
| Segmental | Cystic disease involving only one pole of one or both kidneys and sparing the remaining renal tissue |
| Asymmetric | Diffuse cystic involvement of one kidney causing marked renal enlargement with mild segmental or minimal diffuse involvement of the contralateral kidney defined by a small number of cysts (>2 but <10) and volume accounting for <30% of TKV |
| Lopsided | Bilateral distribution of renal cysts with mild replacem account for ≥50% TKV (the largest cyst diameter is us |
| B | |
| Bilateral presentation with acquired unilateral atrophy | Diffuse cystic involvement of one kidney causing mo acquired atrophy |
| Bilateral presentation with bilateral kidney atrophy | Impaired renal function (serum creatinine ≥1.5 mg/dl by an average length <14.5 cm, and replacement of k |



## 2.1. Hypertension

**Practice Point 2.1.1:** Management of high blood pressure (BP) in people with ADPKD should include regular BP monitoring, preferably with home BP measurements (HBPM), dietary and lifestyle modifications, and pharmacotherapy, if indicated (Figure 15).

| 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 |

## 2.1. Hypertension

**Recommendation 2.1.3:** For people with ADPKD aged **18–49 years** with chronic kidney disease (CKD) **G1-G2** and high BP (>130/85 mm Hg), we recommend a target BP **≤110/75** mm Hg as measured by HBPM (1D).

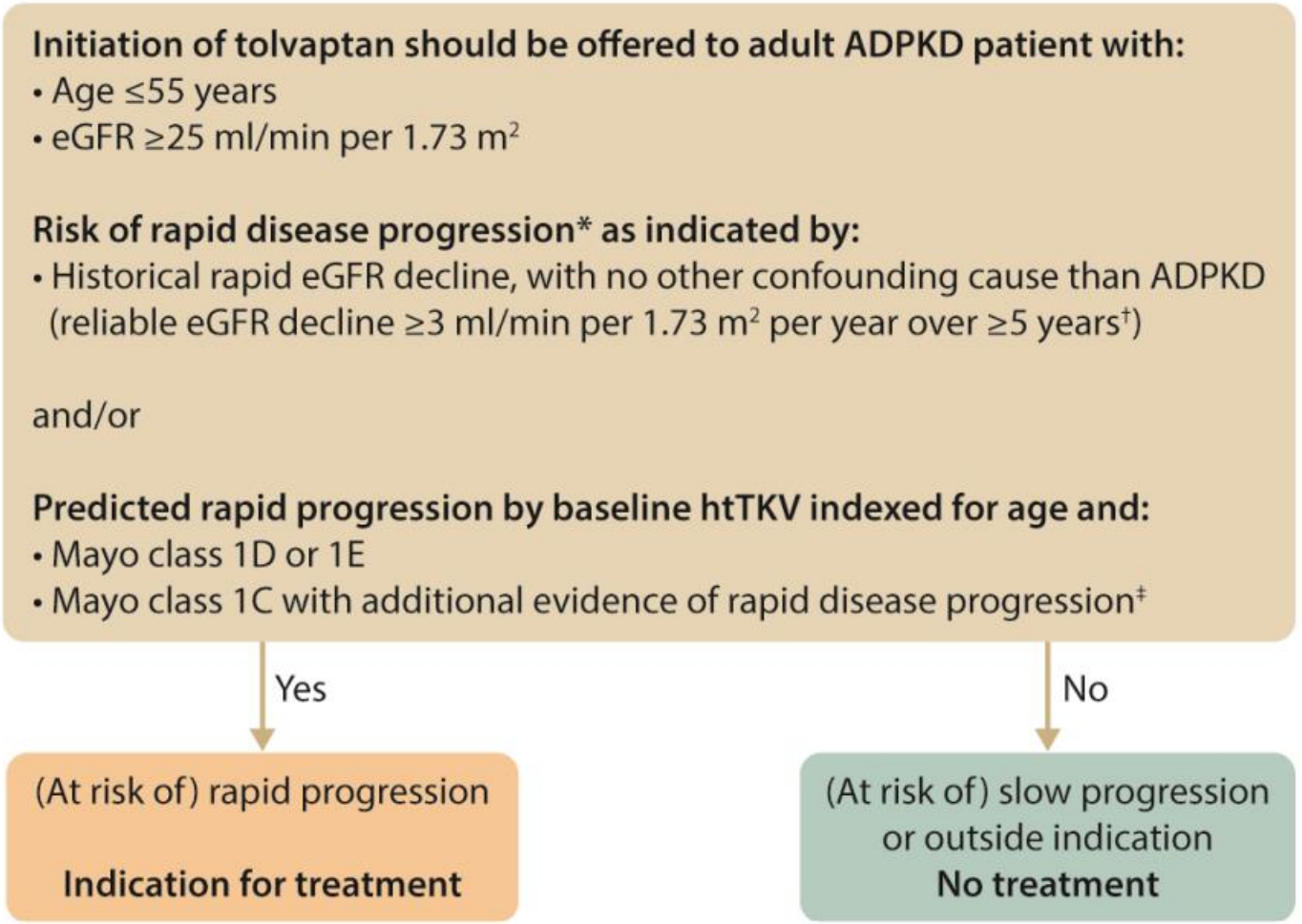
**Recommendation 2.1.4:** For people with ADPKD **≥50 years** of age **and/or** with more advanced CKD (CKD **G3-G5**), we suggest a target mean systolic blood pressure (SBP) **<120** mm Hg, if tolerated, using standardized office blood pressure BP measurement (2B).

**Recommendation 2.1.5:** For people with ADPKD and high BP, we recommend using **renin-angiotensin system inhibitors** (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or **angiotensin II receptor blocker** [ARB]) as first-line treatment to achieve the recommended target BP (1C).

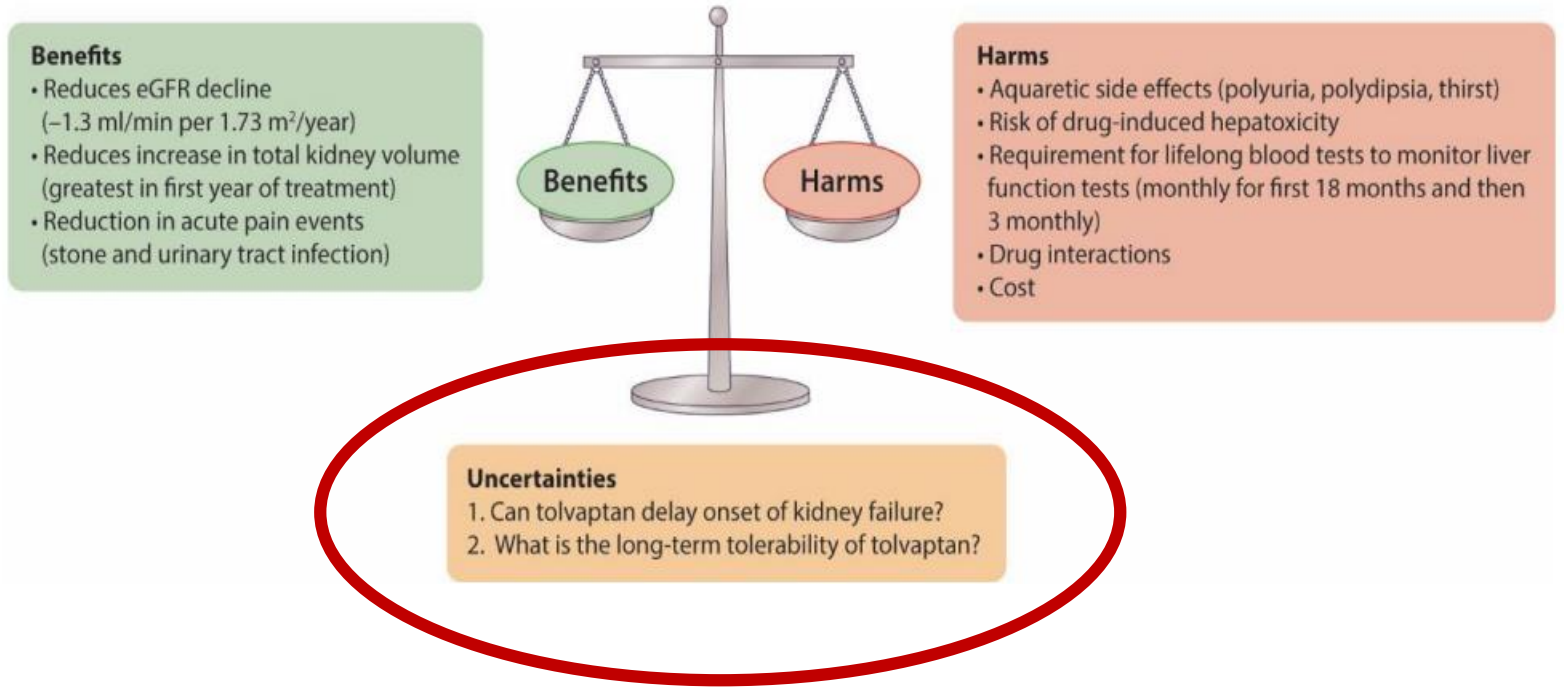
## 4.1. Tolvaptan

### 4.1.1. Indications for tolvaptan in ADPKD

**Recommendation 4.1.1.1:** We recommend initiating tolvaptan treatment in adults with ADPKD **aged 18-55 years** with an estimated glomerular filtration rate (**eGFR**) **≥25 ml/min/1.73 m2** who have or are at risk for **rapidly progressive disease** (Figure 25) (**1B**).



# 4.1. Tolvaptan



## 4.2.1. General advice regarding water intake

**Recommendation 4.2.1.1:** We suggest adapting water intake, spread throughout the day, to achieve **at least 2 liters of urine per day** in people with ADPKD and an eGFR ≥30 ml/min per 1.73 m2 without contraindications to excreting a solute load (**2D**).

| |
|---|
| Baseline hyponatremia (<135 mmol/l) |
| Potential safety risk for increased water intake<br>• Risk of fluid overload (heart failure, cirrhosis)<br>• Requirement for fluid restriction |
| Use of medications that may increase the risk of hyponatremia (SSRIs, TCAs), thiazides used for BP control |

***Table 7. Relative contraindications for increasing water intake.*** SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants

**Practice Point 4.2.2.2:** People with CKD G4-G5 (eGFR <30 ml/min per 1.73 m2) or who have a clinical contraindication to high water intake should drink to thirst and/or follow individualized clinical advice.

NEJM Evidence

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ORIGINAL ARTICLE

# Prescribed Water Intake in Autosomal Dominant Polycystic Kidney Disease

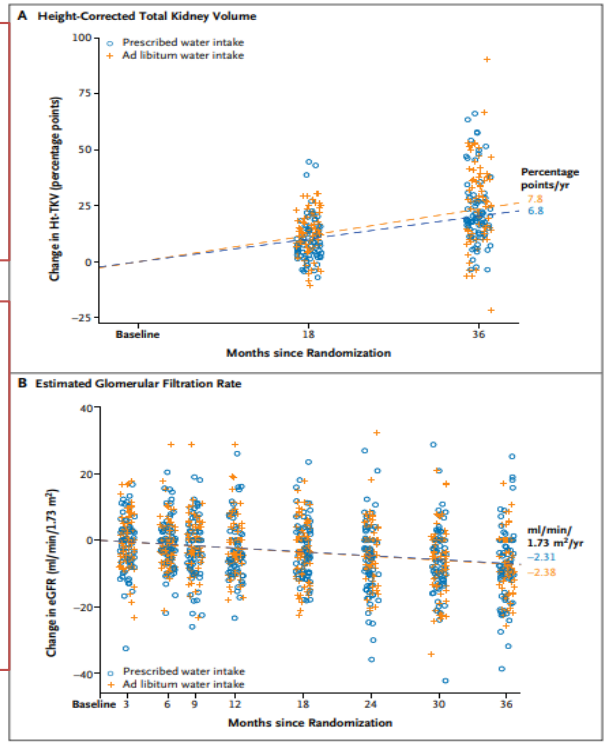
- Τυχαιοποιημένη μελέτη, 3 χρόνων
- 184 ασθενείς με ADPKD, eGFR ≥ 30

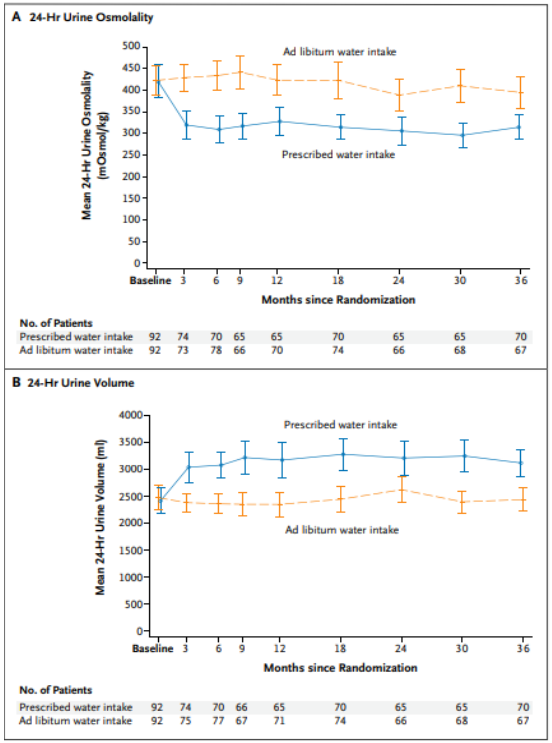
Πρόσληψη νερού ώστε Uosm ≤ 270 mOsmol/kg

VS

Πρόσληψη νερού ad libitum

- **Καμία διαφορά** στον ετήσιο ρυθμό μεταβολής του TKV και στο eGFR στα 3 έτη
- **Χαμηλά ποσοστά συμμόρφωσης** στην ομάδα υψηλής πρόσληψης νερού
- 52% μόνο πέτυχε το στόχο Uosm ≤ 270 (ως μέση τιμή στα 3 έτη)
- <50% πέτυχε μέση αποβολή ούρων > 3 L/d



## 4.6. Somatostatin analogues

**Recommendation 4.6.1:** We suggest that somatostatin analogues should be prescribed only in people with ADPKD with **severe symptoms due to massively enlarged kidneys** to lower the growth rate of kidney cysts when no better options are available(**2B**).

Although somatostatin analogues **do not have clear kidney-protective effects**, there may be a role for these agents in reducing volume-related complaints in ADPKD, especially in people with a **high combined polycystic kidney and liver volume**.

# Ανάλογα σωματοστατίνης στην ADPKD

- Ισχυρά προκλινικά δεδομένα
- Θετική επίδραση στη μείωση του όγκου των **ηπατικών** κύστεων, κυρίως τον 1ο χρόνο της θεραπείας και σε γυναίκες < 48 έτη
- **ALADIN 1 Study** (Caroli et al. Lancet 2013)
  - Πολυκεντρική ιταλική μελέτη, octreotide long-acting release (LAR) IM vs placebo
  - 75 ασθενείς με ADPKD, οι περισσότεροι με eGFR >60 mL/min/1.73 m2
  - στα 3 έτη **καμία διαφορά στην αύξηση TKV και στο GFR**
- **ALADIN 2 Study** (Perico N. PLoS Med 2019)
  - eGFR 15-40 mL/min/1.73 m2
  - στα 3 έτη **καμία διαφορά στο GFR**, επιβράδυνση ↑ κύστεων, **↓ προόδου σε ΧΝΝΤΣ**, **↓ doubling SCreat**

→ **Έγκριση στην Ιταλία**

- **DIPAK 1 RCT** (JAMA. 2018)
  - 309 ασθενείς με ADPKD και eGFR 30-60 mL/min/1.73 m2
  - Lanreotide 120 mg sc κάθε 4 εβδομάδες για 2.5 χρόνια vs. usual care
  - μείωση στην ετήσια αύξηση του TKV (4.1 vs 5.6 %)
  - **Καμία επίδραση στο eGFR** (3.6 vs 3.5 mL/min/1.73 m2 ετήσια μείωση)

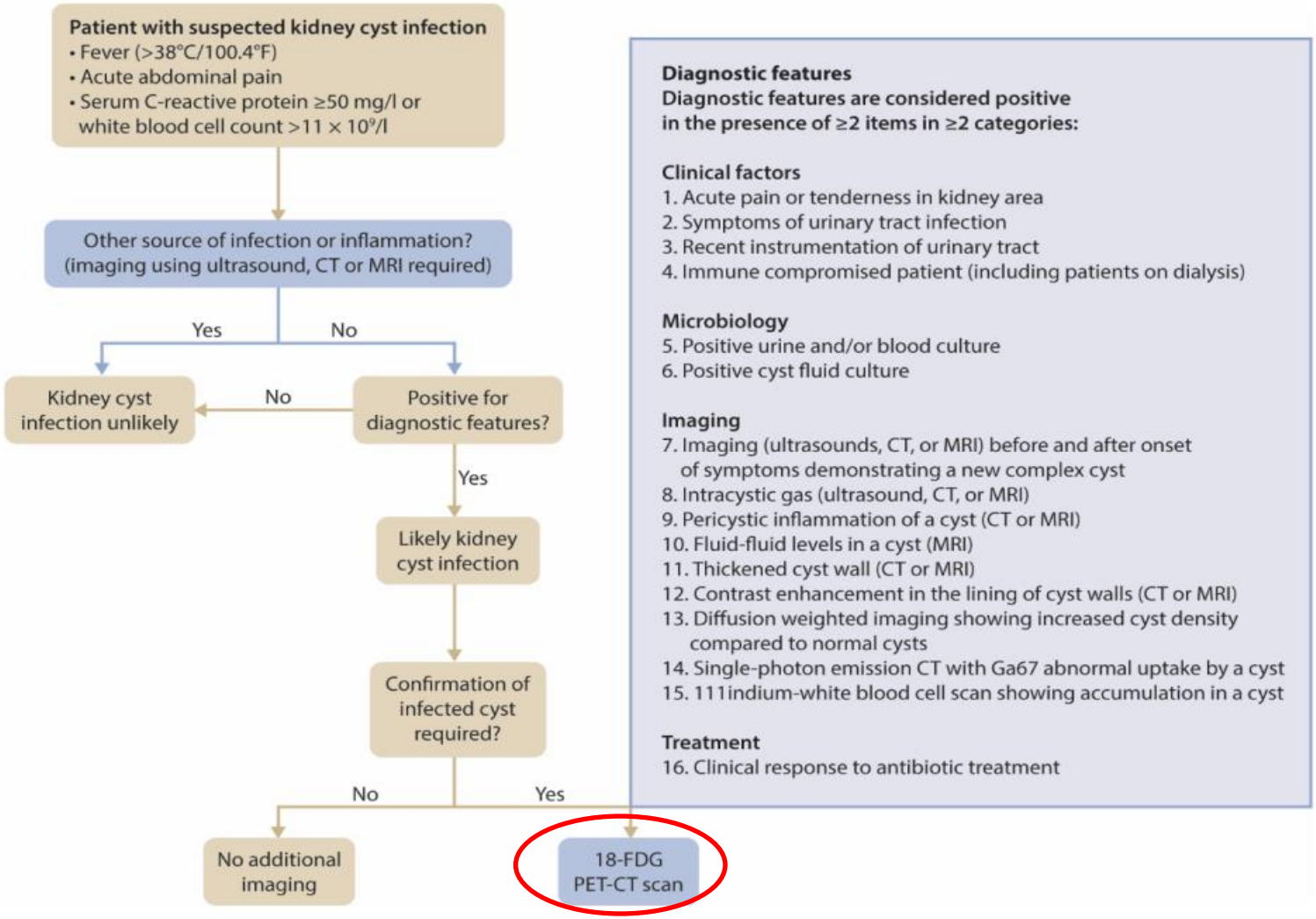
## Somatostatin analogues in PLD

**Recommendation 5.2.3.1:** We suggest prescribing long-acting somatostatin analogues in people with ADPKD and **markedly enlarged polycystic liver with severe volume related symptoms** (**2B**).

**Practice Point 5.2.3.3:** When long-acting somatostatin analogues are prescribed, the effect on symptom burden and/or volume of polycystic liver and kidneys should be evaluated after 6 months. When beneficial effects of therapy are not observed, somatostatin analogues should be discontinued.

## 2.6. Urinary tract infections

**Practice Point 2.6.4:** People with ADPKD who present with fever, acute abdominal or flank pain, and increased white blood cells and/or C-reactive protein (CRP) should be worked up for **kidney cyst infection** (Figure 17).



## 2.6. Urinary tract infections

**Recommendation 2.6.5:** In people with ADPKD and kidney cyst infection, we suggest treatment with **4–6 weeks** of antibiotic therapy rather than a shorter course (2D).

**Practice Point 2.6.5:** A **lipid-soluble antibiotic** (e.g., fluoroquinolones, trimethoprim-sulfamethoxazole) should be used to treat kidney cyst infection in ADPKD, if possible.

# Aneurysms and ADPKD: The importance of providing detailed information

**Recommendation 6.1.1:** We recommend **informing** adults with ADPKD about increased risk for intracranial aneurysms (ICA) and subarachnoid hemorrhage (1C).

- *Practice Point 6.1.1.* All people with ADPKD should be educated to recognize **thunderclap headache** which should prompt immediate medical attention.
- *Practice Point 6.1.2:* A detailed **personal history** of SAH and a **family history** of ICA, SAH, and **unexplained sudden death** should be obtained to identify people with ADPKD at higher risk for ICA.
- *Practice Point 6.1.3:* Because **tobacco exposure** is a strong modifiable factor for ICA development and rupture, clinicians should ask all people with ADPKD about their tobacco use, advise them to stop using tobacco, and provide behavioral interventions and approved pharmacotherapy for cessation, if needed
- *Practice Point 6.1.4:* Because **uncontrolled hypertension** is a strong modifiable factor for ICA development and rupture, early diagnosis and adequate treatment of hypertension is indicated in people at risk of or diagnosed with ADPKD, particularly in those at an increased risk for ICA

**Practice Point 6.1.5.** People should be informed of the implications of ICA screening

| Advantages | Limitations |
|---|---|
| • May allow adequate intervention if an ICA at risk of rupture is identified, allowing to prevent death or significant comorbidity.<br>• May reduce anxiety and provide reassurance when no ICA is detected | • Likely to identify ICA with very low risk of rupture (≤5 mm/anterior circulation) and which do not require intervention but require long-term follow-up<br>• Does not exclude the risk of *de novo* ICA development and rupture after screening<br>• May lead to procedures with possible treatment failure or complications, including death or significant morbidity<br>• May cause anxiety when an ICA is identified<br>• May limit access to life insurance, loans, or driving licenses<br>• May limit work opportunities<br>• Cost associated with screening |

***Table 13. Advantages and limitations of screening for unruptured intracranial aneurysms (ICA).***

# ICA: Recommendations for screening

**Recommendation 6.1.2.** We recommend screening for ICA in people with a **personal history of SAH** or a **positive family history of ICA, SAH, or unexplained sudden death** if the person will be eligible for treatment and has **reasonable life expectancy** (1D).

**Practice Point 6.1.6.** Screening for unruptured ICA should also be discussed in people with de novo ADPKD, those with unknown familial history or small number of ADPKD-affected relatives, and in those with personal or familial history of extracerebral vascular phenotype.

**Practice Point 6.1.7.** Screening for unruptured ICA may also be considered in specific clinical settings, such as in the context **of evaluation for kidney and/or liver transplantation** or before **major elective surgery**.

**Practice Point 6.1.8.** People with ADPKD who are not considered at increased risk for ICA and who, after comprehensive information, prefer being screened for ICA should be given access to screening.

In **women with ADPKD** and either a **family history of ICA, SAH, or unexplained sudden death**; de novo ADPKD; unknown familial history; or a small number of ADPKD-affected relatives, screening for unruptured ICA should **precede pregnancy planning**.

Screening before adulthood is usually not advised.

Figure 40. **Nutrition guideline** for people with autosomal dominant polycystic kidney disease (ADPKD) and chronic kidney disease (CKD) **G1–G4**.

| | Recommended daily intake | Comments and impact on ADPKD |
|---|---|---|
| **Water** | ≥2 l/day | High water intake prevents kidney stones and may reduce kidney function loss.<br>May need to adjust daily intake depending on concomitant medications, capacity for voiding, and to minimize the risk of hyponatremia. |
| **Salt** | Sodium <2 g/day (equivalent to <90 mmol sodium/day or <5 g salt/day) | Recommended by WHO for the general population.[6]<br>High salt intake in the observational CRISP (Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease) study and in post hoc analyses of clinical trials in patients with ADPKD has been associated with faster increase in kidney volume and, at later stages (eGFR 25–60 ml/min/1.73 $m^2$), with faster decline in kidney function.[7–9]<br><br>Patients should be counseled not to add salt to their food, and to avoid processed foods (typically high in sodium) as much as possible. |
| **Protein** | 0.8–1 g/kg (weight)/day | Recommended by WHO for general population.[10]<br><br>Increase plant-based protein, compared to animal sources<br><br>Benefit of protein restriction has not been demonstrated; however, excess dietary protein (≥1.3 g/kg/day) may be harmful. |
| **Calories** | 25–35 kcal/kg/day, individualized to treat or prevent overweight and obesity | High BMI and obesity are associated with many adverse health conditions and may be associated with accelerated ADPKD progression.[11,12] |
| **Fat** | <30% of daily energy intake<br>Saturated fat limited to <10% of total fat | Recommended for general population[13–15] |
| **Fiber** | 25–38 g/day (14 g per 1000 calories) | Recommended for general population[16] |
| **Caffeine** | <400 mg/day | Recommendation by WHO for general population[16,17] |
| **General** | A well-balanced diet:[1]<br>• high in vegetables, fruits, whole grains, fiber, legumes, plant-based proteins, unsaturated fats, and nuts<br>• low in processed meats, refined carbohydrates, and sweetened beverages. | Recommended by WHO for general population[4]<br><br>At least 400 g (5 portions per day) of fruit and vegetables, excluding high-starch foods such as potatoes.<br><br>More specific information on recommended food amounts can be found in the Dietary Guidelines for Americans 2020–2025[16] |

# Calculating BMI in ADPKD patients

**Practice Point 7.1.5:** When calculating BMI, clinicians should take into account the weight of enlarged kidneys and liver.

**Adjusted body weight** = measured body weight (kg) minus TKV (in kg) minus TLV (in kg) plus weight of normal kidneys (kg) and liver (kg)

This calculation assumes that 1 ml of kidney or liver volume is equivalent to 1 g of weight.

## CHAPTER 8. PREGNANCY AND REPRODUCTIVE ISSUES

### Hormone therapy

**Practice Point 8.1.2:** Since **estrogen** and possibly progesterone exposure may associate with an increased risk of PLD progression, women with ADPKD and liver cysts should be educated regarding their contraceptive choices.

Estrogen-based and combined hormonal contraception can be used under supervision in people with mild PLD but should be avoided in people with moderately severe or severe PLD.

Intravaginal rings, intrauterine devices and gestagen oral contraceptives may be preferred for women with PLD.

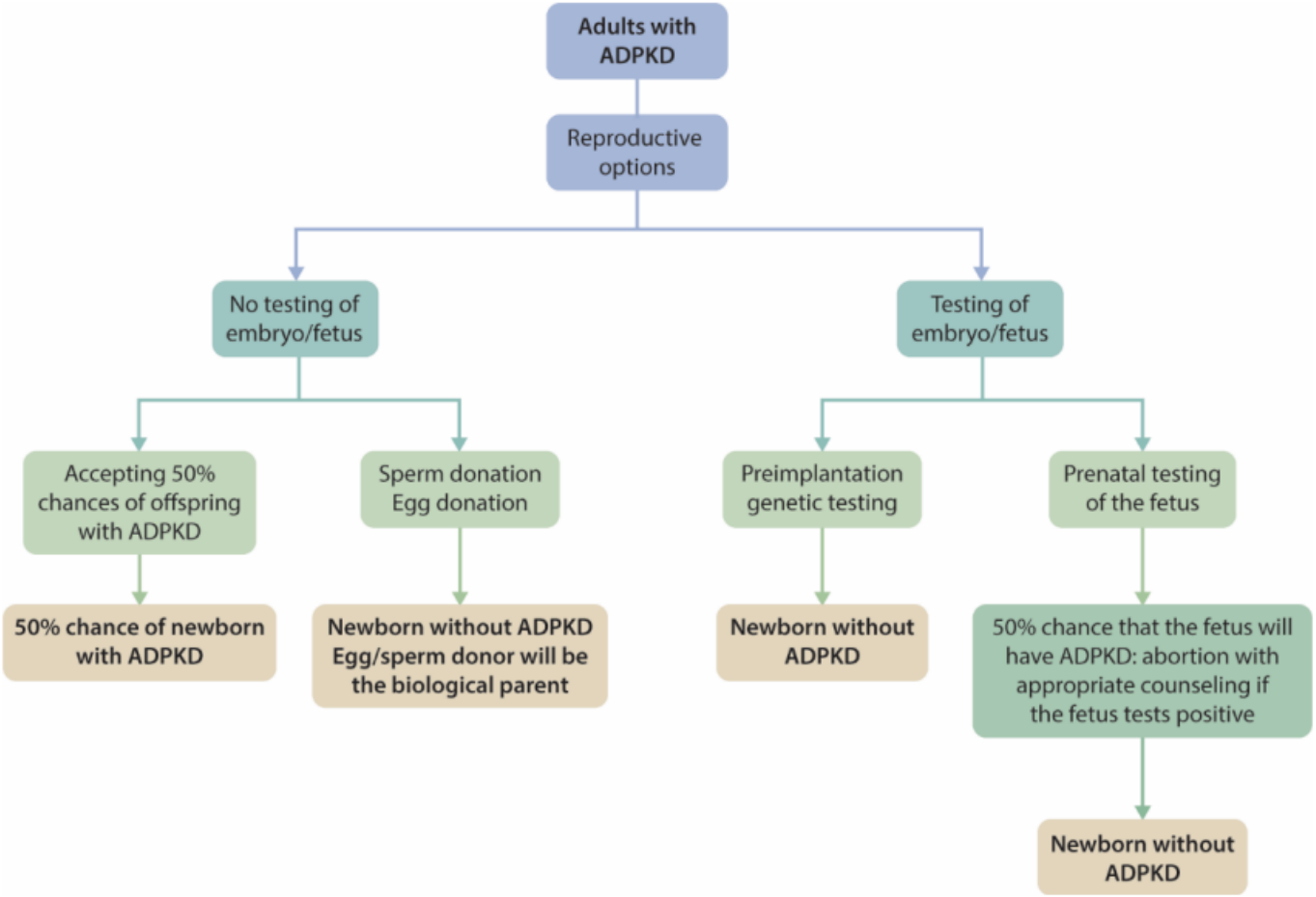
**Practice Point 8.1.4:** When considering hormone therapy in women with ADPKD, **liver imaging** should be made available to inform discussion about options for contraception, hormonal replacement, and other indications.

## 8.2. Preconception counseling

**Practice Point 8.2.4:** Tolvaptan, RASi (i.e., ACEi and ARBs), and any other teratogenic drug should be stopped prior to pregnancy and not restarted until the mother has completed breastfeeding.

## 8.2. Preconception counseling

**Practice Point 8.2.3:** People with ADPKD at reproductive age should be offered appropriate counseling and all available reproductive options



## 8.5. Preeclampsia

**Practice Point 8.5.1:** Women with ADPKD are at an increased risk of preeclampsia and preterm delivery and should be carefully monitored throughout their pregnancy and in the postpartum period.

**Practice Point 8.5.2:** Low-dose aspirin (75–150 mg daily) should be prescribed from week 12 to week 36 in pregnant women with ADPKD.

# CHAPTER 9. PEDIATRIC ISSUES

## 9.1. Diagnosis of ADPKD in children

**Practice Point 9.1.2: Shared decision-making** and a **family-centered approach** should be undertaken when discussing the **benefits and harms related to diagnosis** of **at-risk children in families with ADPKD**, including the parents/legal guardians and the mature child.

**Practice Point 9.1.4:** When diagnosis of ADPKD in children is desired, use **ultrasound** as the preferred imaging method.

**Practice Point 9.1.7:** In children with **kidney cysts and negative family history** for ADPKD who seek diagnosis, perform **ultrasound of the parents** (or grandparents if parents <40 years).

**Practice Point 9.1.9:** Offer genetic testing for **children with VEO-ADPKD** or **atypical presentation** of ADPKD.

**Practice Point 9.1.10:** Offer genetic testing for children with cystic kidneys and a **negative familial history** of ADPKD.

## CHAPTER 9. PEDIATRIC ISSUES

### 9.2. BP control in children and adolescents with ADPKD

**Practice Point 9.2.1:** Assess **standardized office BP annually** in children and adolescents **with and at risk for ADPKD**.

**Practice Point 9.2.5: Echocardiography** should be performed to exclude left ventricular hypertrophy (LVH) in children and adolescents with ADPKD and high BP.

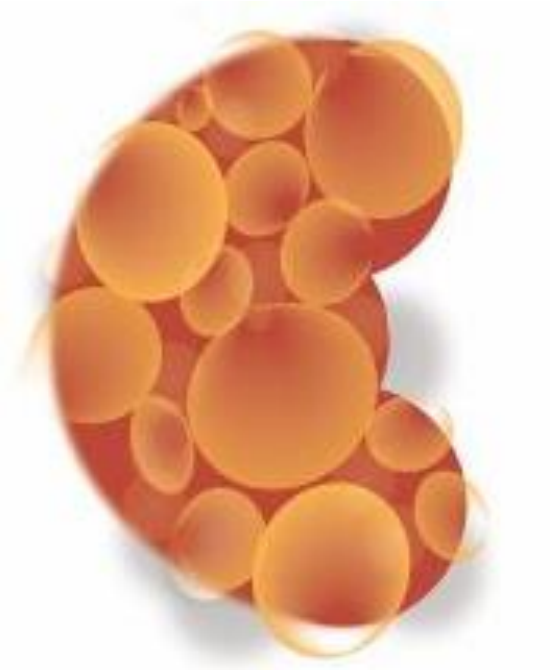
**Recommendation: 9.2.1:** We recommend targeting **BP to ≤50th percentile** for age, sex, and height or **≤110/70 mm Hg** in adolescents in the setting of ADPKD and high BP (1D).

**Recommendation 9.2.2:** We **recommend use of RASi** (i.e., ACEi or ARBs) as the first-line pharmacological therapy for high BP in children and adolescents with ADPKD (1D).

## CHAPTER 9. PEDIATRIC ISSUES

### 9.5. Optimal models of care for children with ADPKD

**Practice Point 9.5.3:** There is currently **insufficient evidence to support use of targeted or disease-modifying therapies** for ADPKD in children beyond antihypertensive treatment.



**Ευχαριστώ για την προσοχή σας**

# ΓΕΝΕΤΙΚΗ ADPKD

- Πέραν των γονιδίων PKD1 και PKD2, τουλάχιστον 7 ακόμη γονίδια έχει βρεθεί να σχετίζονται με ADPKD
- Ο γονιδιακός έλεγχος σε ασθενείς με ADPKD αναδεικνύει παθογόνες ή δυνητικά παθογόνες μεταλλάξεις στο 75% των περιπτώσεων
- Συχνά ανιχνεύονται μόνο παραλλαγές με αβέβαιη σημασία (variants of uncertain significance)
- Σε αυτές τις περιπτώσεις, εφόσον ο φαινότυπος είναι συμβατός με ADPKD και δεν υπάρχουν κλινικά ή γενετικά δεδομένα υπέρ άλλης κυστικής νόσου, ο ασθενής συνεχίζει να φέρει την κλινική διάγνωση της ADPKD
- Οι μεταλλάξεις στο γονίδιο PKD1 διακρίνονται σε αυτές που προκαλούν αποκοπή του πρωτεϊνικού προϊόντος (truncating) και αναμένεται να έχουν σημαντική επίδραση στη λειτουργία του γονιδίου και σε αυτές που δεν προκαλούν (non-truncating)

## 3.2. Kidney transplantation

**Practice Point 3.2.6:** During the pre-transplantation work-up for candidates with ADPKD, the **total kidney and liver weight derived from total kidney and liver volumes should be calculated and subtracted from the patient's total body weight** for a more accurate assessment of weight and BMI.

**Recommendation 3.2.1:** We suggest that **native kidney nephrectomy** in people with ADPKD receiving a kidney transplant should be performed **only for specific indications where the benefit outweighs the risk** (Figure 22) (2C).

**Recommendation 3.2.2:** We suggest **unilateral rather than bilateral** native kidney nephrectomy in people with ADPKD, when appropriate (2D).

**Recommendation 3.2.3:** We suggest that kidney transplant candidates with ADPKD who require **native kidney nephrectomy** undergo the procedure **at the time of or after**, but **not before**, transplantation, whenever possible (2C).

**Practice Point 3.2.10: Evaluation for RCC** in pretransplant people with ADPKD should be individualized and imaging of the kidneys (e.g., **abdominal MRI**) **within 1 year** prior to transplantation should be considered.

**TEMPO 3:4** — **CKD G1–G2**

**Study population**
n=1445
18 to 50 years old
TKV >750 ml in CKD

**Dose of tolvaptan**
120 mg/d (55%), 90 mg/d (21%), 60 mg/d (24%)

**Main results**
- Primary endpoint: reduced rate of increase in TKV: 2.8%/year in tolvaptan group vs. 5.5%/year in placebo
- Secondary endpoint: slower decline in kidney function (reciprocal of the serum creatinine level, −2.61 [mg/ml]/year vs. −3.81 [mg/ml]/year, P <0.001); lower rates of worsening kidney function (2 vs. 5 events per 100 person-years, P <0. 001) and kidney pain (5 vs. 7 events per 100 person-years of follow-up; P=0.007).

**Adverse effects**
Tolvaptan associated with aquaresis and abnormal liver function tests and higher discontinuation rate (23% vs. 14% in the placebo group).

**REPRISE** — **CKD G3–G4**

**Study population**
n=1390
18–55 years old + (eGFR 25–65 ml/min per 1.73 $m^2$)
56–65 years old + (eGFR 25–44 ml/min per 1.73 $m^2$)

Ability to tolerate tolvaptan after an 8-week run-in

**Dose of tolvaptan**
120 mg/d (61%), 90 mg/d (30%), 60 mg/d (10%)

**Main results**
- Primary endpoint: Reduced rate of decline in eGFR by −2.34 ml/min per 1.73 $m^2$ in the tolvaptan vs. −3.61 ml/min per 1.73 $m^2$ in the placebo; P <0.001).

**Adverse effects**
Reversible increases in the ALT (to >3 times normal range)
5.6% in tolvaptan group vs. 1.2% in the placebo group

## 4.1. Tolvaptan

### 4.1.1. Indications for tolvaptan in ADPKD

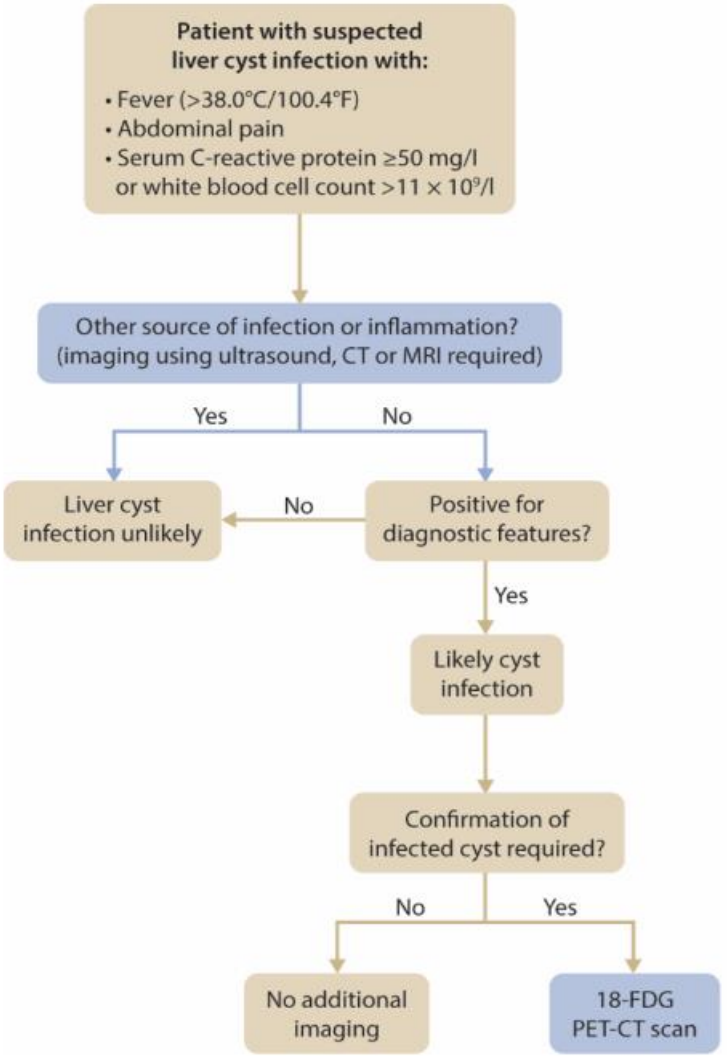
**Practice Point 4.1.1.2:** To determine eligibility for tolvaptan treatment, **rapid disease progression** is defined as a confirmed annual **eGFR decline ≥3 ml/min per 1.73 m2** , based on **≥5 measurements over a period of ≥5 years**. Evidence for rapid disease progression is also present if a person with ADPKD has CKD G3-G5 before age 45 years, enlarged kidneys, and no other explanation for reduced kidney function.

**Practice Point 4.1.1.3:** The Mayo Imaging classification, based on MRI, should be used as the primary imaging method for risk prediction and in consideration of tolvaptan in routine clinical care.

## 5.3. Liver cyst infections

### 5.3.1. Diagnosis

**Practice Point 5.3.1.1:** Diagnosis of liver cyst infections should utilize culture data, advanced imaging, and clinical signs and symptoms




**Diagnostic features**
**Diagnostic features are considered positive in the presence of ≥2 items in ≥2 categories.**

**Clinical factors**
1. Pain presenting as acute pain or tenderness in liver area
2. History of cyst infection
3. Recent instrumentation of biliary tract
4. Immune compromised patient (including patients on dialysis)

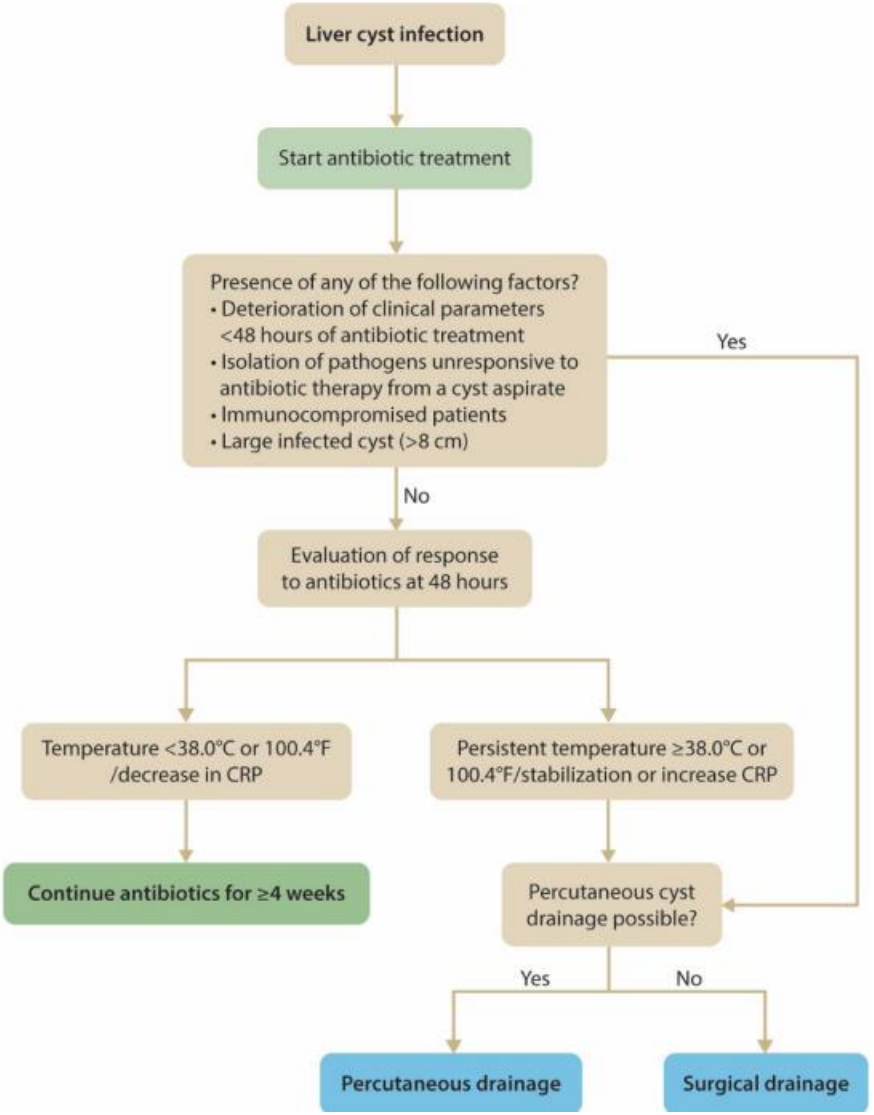
**Microbiology**
5. Positive blood culture
6. Positive cyst fluid culture

**Imaging**
7. Imaging showing changes before and after onset of symptoms (ultrasound, CT or MRI)
8. Intracystic gas (ultrasound, CT or MRI)
9. Pericystic inflammation of a cyst (CT or MRI)
10. Fluid-fluid levels in a cyst (MRI)
11. Thickened cyst wall (CT or MRI)
12. Contrast enhancement in the lining of cyst walls (CT or MRI)
13. Diffusion weighted imaging showing increased cyst density compared to normal cysts
14. Single-photon emission CT with Ga67 abnormal uptake by a cyst
15. 111indium-white blood cell scan showing accumulation in a cyst

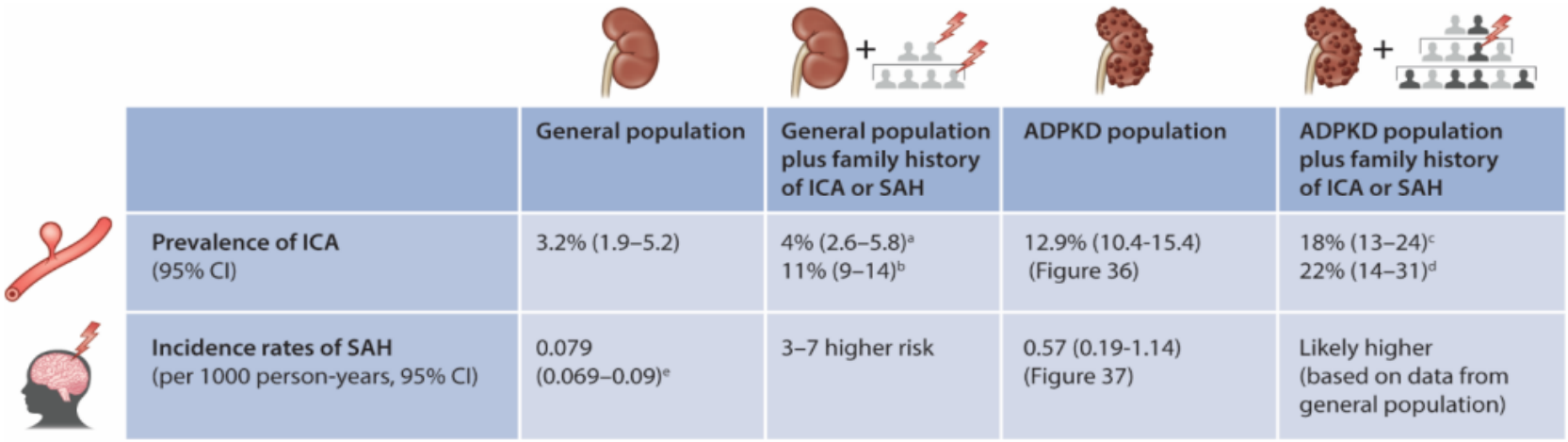
**Treatment**
16. Clinical response to antibiotic treatment

# Figure 34. Management of liver cyst infections.

### 5.3.2. Management



# Aneurysms and ADPKD: Epidemiology



| | 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) |

**Prevalence of ICA: 12.9%**

**Incidence of SAH: 0.57 per 1000 person-year = 1 in 1754 patients per year**

# Aneurysms and ADPKD: Risk factors

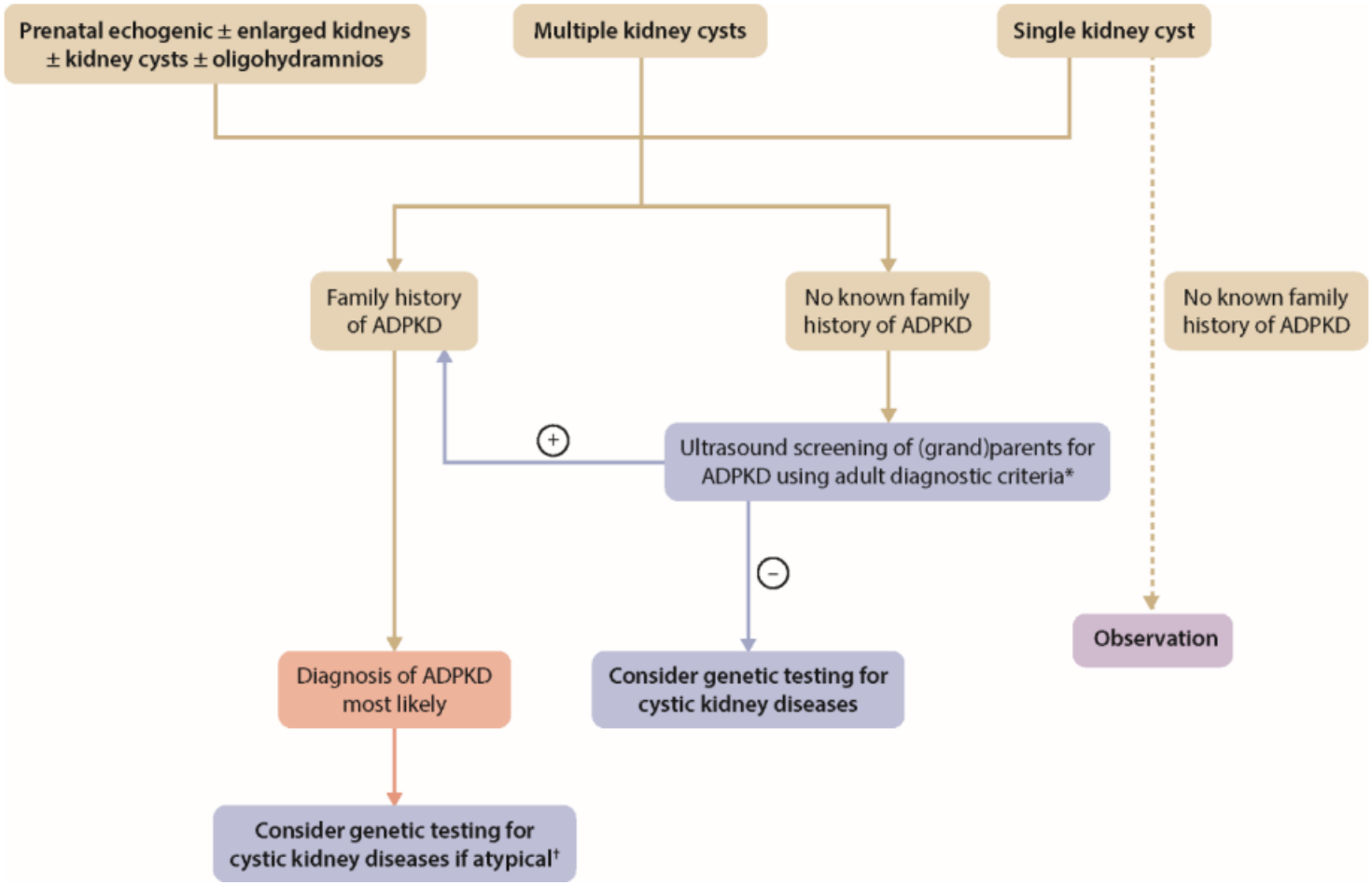
| | **Predictors for prevalent ICA or rupture of ICA and strength of the association** |
|---|---|
| Evidence for association with ICA/SAH in ADPKD population | • Family history of SAH or ICA (stronger association when first-degree relative) – *Strong*<br>• Personal history of SAH or ICA – *Strong*<br>• Female sex – *Moderate*<br>• *PKD1* genotype - *Moderate*<br>• Tobacco smoking (especially >20 pack-years) - *Strong*<br>• Uncontrolled hypertension - *Moderate*<br>• Early onset hypertension (<35y) - *Moderate*<br>• Severity of ADPKD – *Weak* |
| Evidence in non-ADPKD population | • Japanese or Finnish ancestry<br>• Alcohol in large quantity (risk factor for ICA rupture) |

# ICA: Recommendations for screening

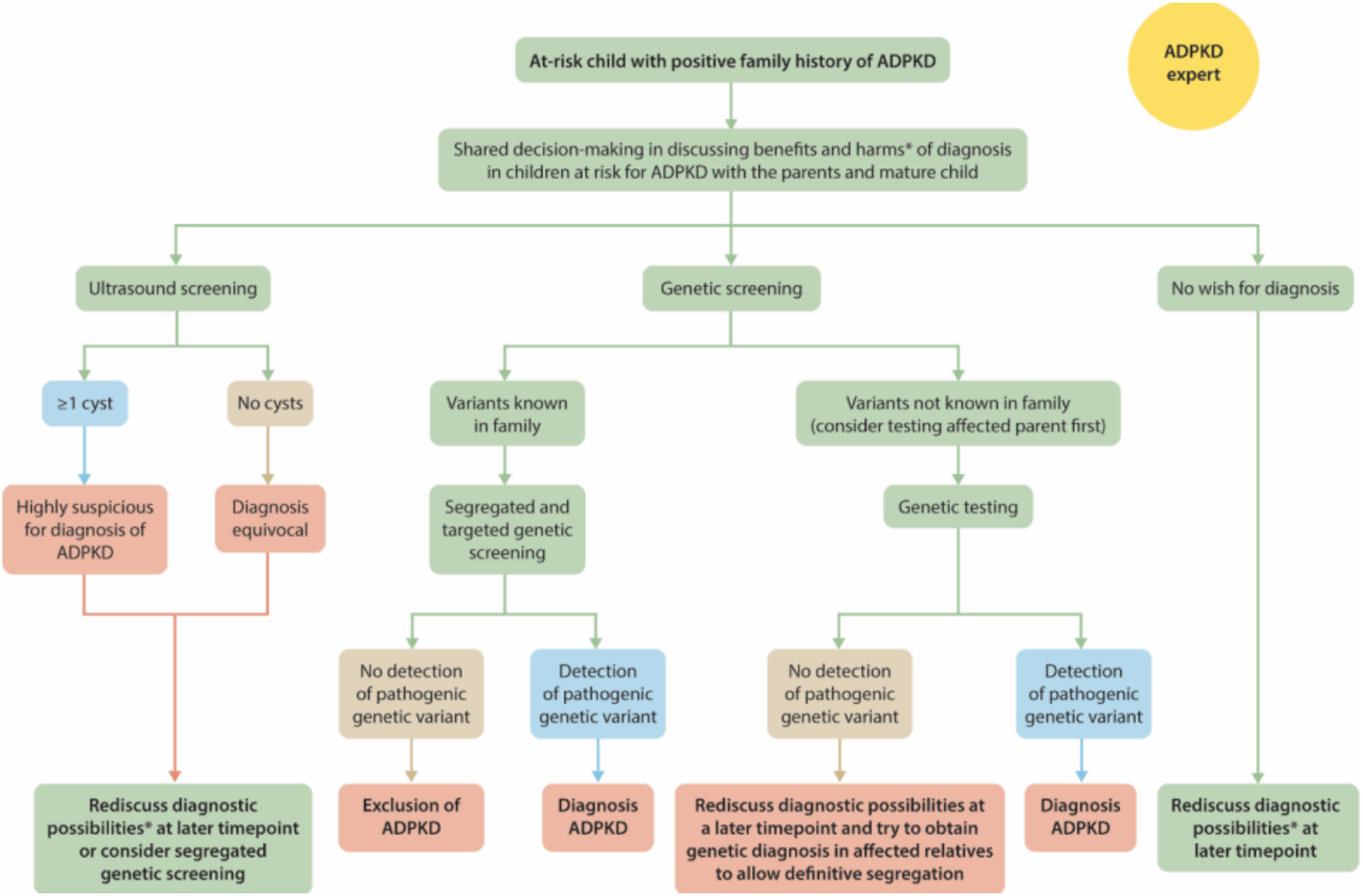
**Practice Point 6.1.10:** If the screening is negative in people with high-risk of ICA, timing of rescreening should be individualized based on risk factors, age, and life expectancy.

In high-risk individuals with good life expectancy rescreening at 5-10 y intervals is advised.

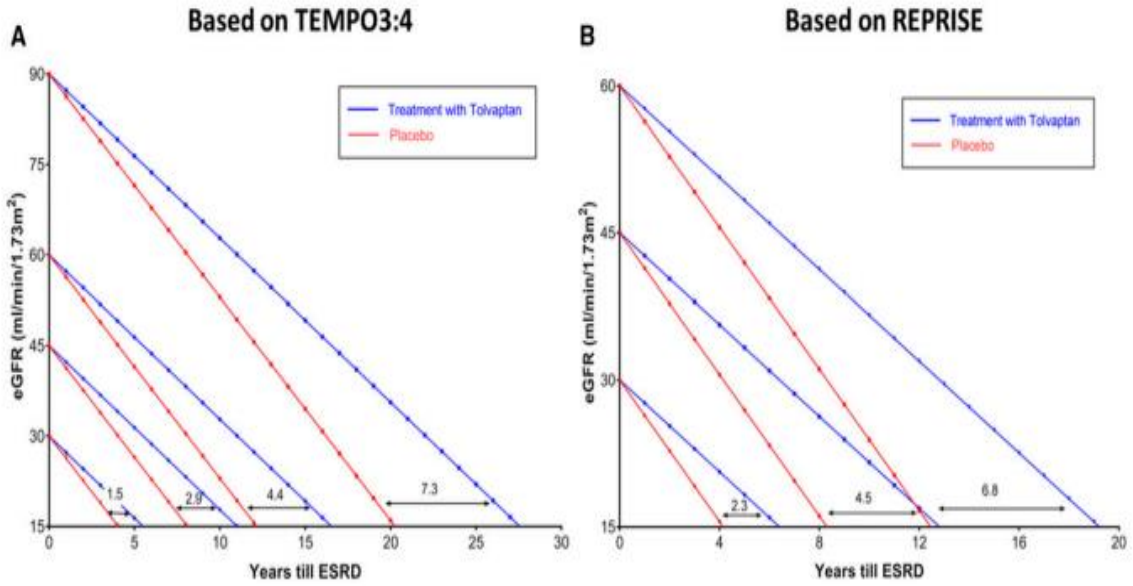
# Diagnosis of children with suspicion of ADPKD



# Diagnosis of children at risk of ADPKD



## Τολβαπτάνη: πόσο καθυστερεί η επέλευση ΤΣΧΝΝ ανάλογα με το eGFR κατά την έναρξη της θεραπείας



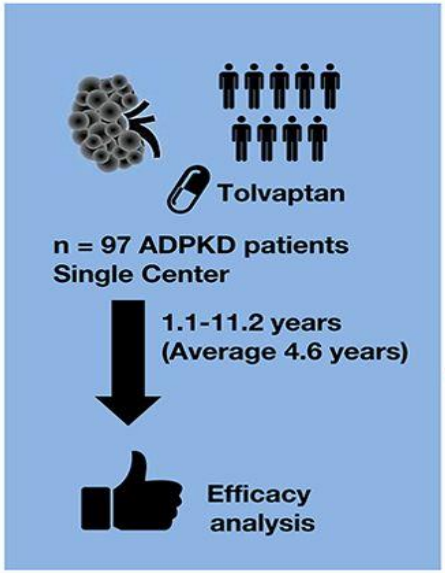

Η θεραπεία με τολβαπτάνη μπορεί να καθυστερήσει την επέλευση ΤΣΧΝΝ από 6-9 χρόνια ή και περισσότερο αν αρχίσει σε πρώιμα στάδια

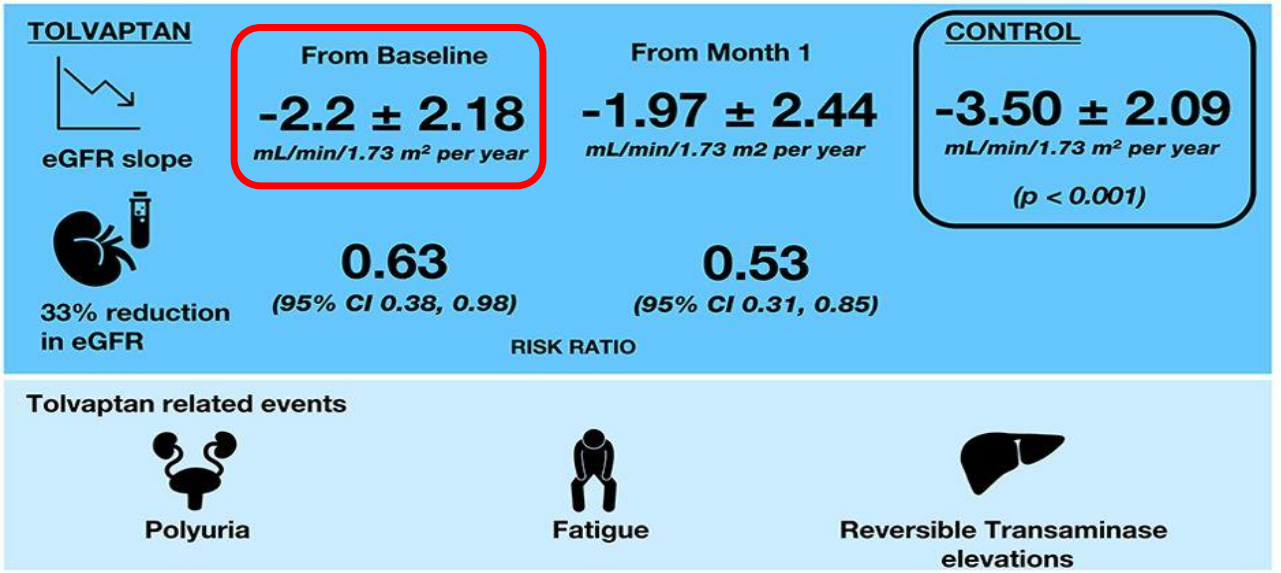
3 χρόνια θεραπείας με τολβαπτάνη (costing ~98 000 euros) παρατείνει το ΤΣΧΝΝ κατά 1 χρόνο

Chebib F, et al. JASN 2018

# Long-term administration of tolvaptan in autosomal dominant polycystic kidney disease

CJASN
Clinical Journal of American Society of Nephrology




**Conclusions** Follow-up for up to 11.2 years (average 4.6 years) showed a sustained reduction in the annual rate of eGFR decline in tolvaptan treated patients compared to controls and an increasing separation of eGFR values over time between the two groups.

Marie Edwards, Fouad Chebib, Maria Irazabal, Troy Ofstie, Lisa Bungum, Andrew Metzger, Sarah Senum, Marie Hogan, Ziad El-Zoghby, Timothy Kline, Peter Harris, Frank Czerwiec, and Vicente Torres. ***Long-term Administration of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease.*** CJASN doi: 10.2215/CJN.01520218

**Marie E. Edwards et al. CJASN 2018;13:1153-1161**

©2018 by American Society of Nephrology

JAMA | Original Investigation

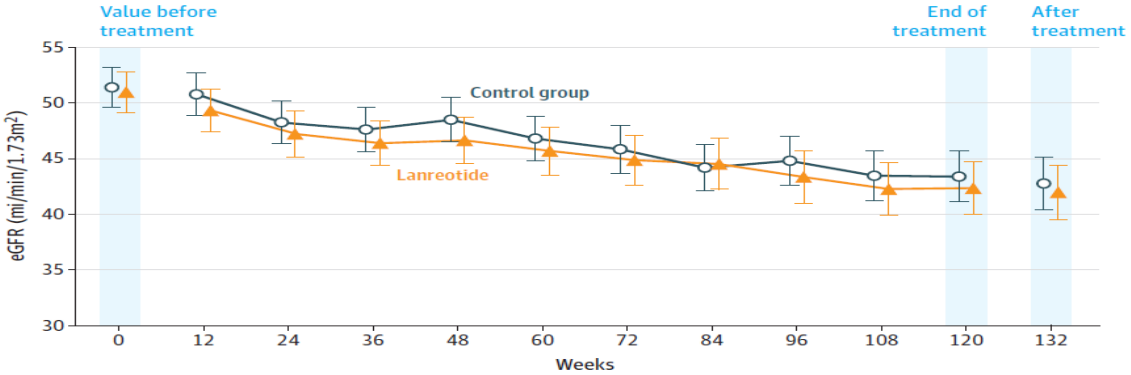
# Effect of Lanreotide on Kidney Function in Patients With Autosomal Dominant Polycystic Kidney Disease

## The DIPAK 1 Randomized Clinical Trial

- 309 ασθενείς με ADPKD και **eGFR 30-60** mL/min/1.73 $m^2$
- Lanreotide 120 mg sc κάθε 4 εβδομάδες για 2.5 χρόνια vs. usual care

Αποτελέσματα

- μείωση στην ετήσια αύξηση του TKV (4.1 vs 5.6 %)
- Καμία επίδραση στο eGFR (3.6 vs 3.5 mL/min/1.73 $m^2$ ετήσια μείωση)




*JAMA.* ***2018****;320(19):2010-2019*