มหาวิทยาลัยมหิดล
คณะแพทยศาสตร์
ศิริราชพยาบาล

SECONDARY HYPERTENSION / ADPKD

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OUTLINE

- Case vignette
- How to approach secondary hypertension
- Renovascular hypertension
- AD polycystic kidney disease

Case 1

- **A 39-year-old woman presented with intermittent scalp tightness for 6 years.**
  “ปวดตึงศีรษะมา 6 ปี”

- The pain was mild, dull, and episodic, lasting less than 30 minutes and resolving spontaneously.
- She denied weakness, numbness, speech difficulty, visual or hearing changes, dizziness, or gait instability.
- 2 years ago, she also reports intermittent bilateral thigh muscle pain and episodic proximal thigh weakness lasting 7–8 hours, which improves with analgesics.

- **Physical exam.:** BP 170/100 mmHg, BMI 29 kg/m2, CVS/RS/Neuro. system WNL

Further Hx & PE ?
How to approach ?

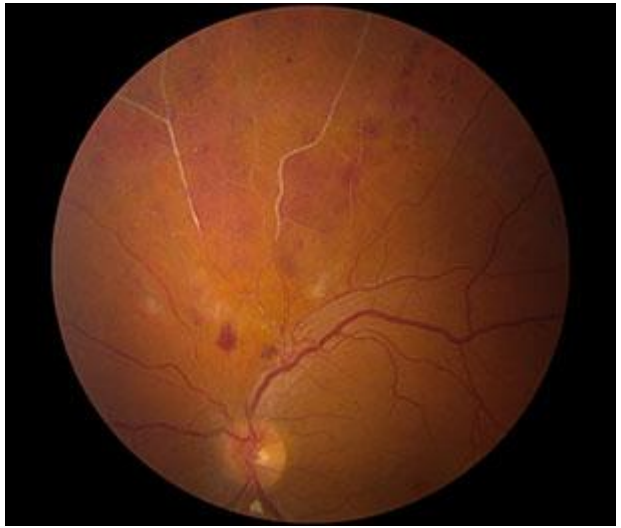
Case 2

- **A 65-year-old man presented with worsening BP control over last 2 months**
  “ความดันโลหิตคุมได้แย่ลง ในช่วง 2 ปี”

- Underlying diseases: T2DM, HT, CAD, CKD G3, PAD
- His BP are now consistently above 150/90 mmHg with bilateral pitting edema.
  Current treatment: “ยาความดัน 4 ชนิด ยาขับปัสสาวะ 1 ชนิด”
- Two months ago: progression of CKD from G3 to G4.
  “หลังปรับเพิ่มยาความดัน”

- **Physical exam.:** BP 160/90 mmHg (all ext.),
  CVS/RS/Neuro. system WNL

Eye exam.? **Further PE ?**
Resistant HT ? **How to approach ?**



Case 3

- **A 40-year-old man presented with hypertension** “ตรวจพบความดันโลหิตสูง”

- **7 years ago**, he was diagnosed with hypertension during hospitalization for a leg fracture and was started on one antihypertensive medication.
- **2 years ago**, his BP became poorly controlled, and he was noted to have worsening kidney function.
- **1 year ago**, his BP became uncontrolled again, and medications were increased.
- He denied hematuria, foamy urine, or changes in urine output at that time; however, he had a history of recurrent right flank pain.

- **Physical exam.:** BP 160/90 mmHg (all ext.), liver span 13 cm., no abdominal bruit, no edema

Further Hx & PE ?
How to approach ?

Secondary hypertension: Approach

1. **Clues to secondary HT**
2. **DDx causes: Clinical**
3. **Review of systems/PE, target organ damage, co-morbidity, drugs**
4. **Investigation**

Hypertension: Definition

AHA/ACC 2025

Categories of Blood Pressure in Adults*

	SBP		DBP
BP Category			
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120 to 129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130 to 139 mm Hg	or	80 to 89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

ESC 2024: BP ≥ 140 or ≥ 90

BP Categories Based on Office and Out-of-Office BP Measurements

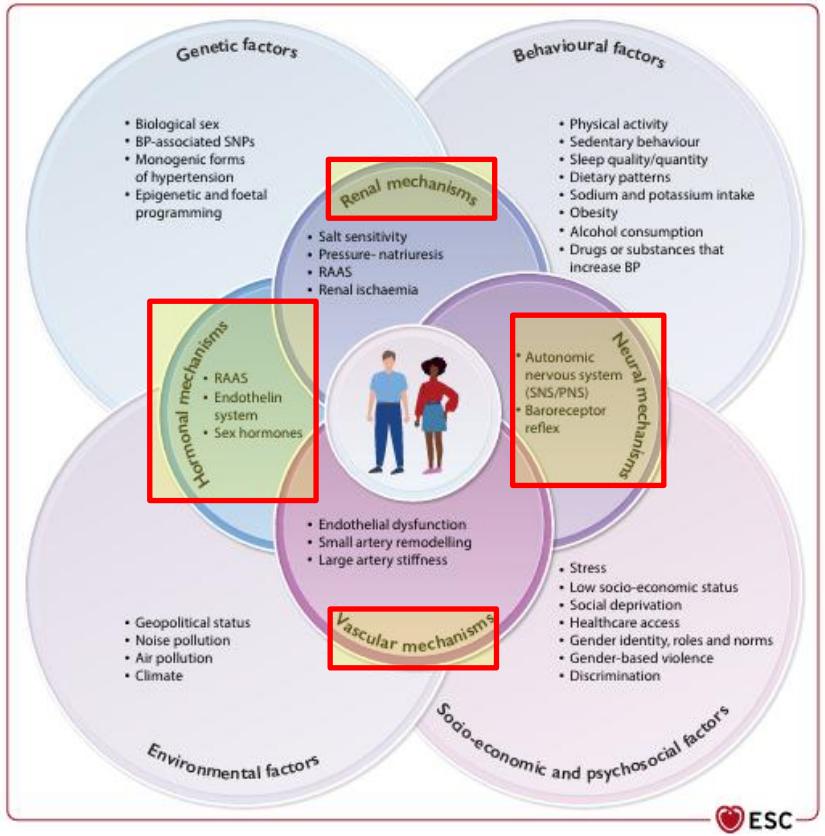
SBP≥130 or DBP≥80

BP Category	High BP in the Office Setting?	High BP Outside of the Office Setting?*
Among individuals not taking antihypertensive medication		
Sustained normotension	No	No
Sustained hypertension	Yes	Yes
Masked hypertension	No	Yes
White-coat hypertension	Yes	No
Among individuals taking antihypertensive medication		
Controlled hypertension	No	No
Uncontrolled hypertension	Yes	Yes
Masked uncontrolled hypertension	No	Yes
White-coat effect	Yes	No

HBPM SBP≥130 or DBP≥80 **ABPM SBP≥125 or DBP≥75**

Hypertension: Definition

Cause of Hypertension



Environmental, Behavioral, and Genetic Causes of Hypertension

Dietary Intake Factors	Nondietary Factors
Higher sodium intake	Genetic variants
Lower potassium intake	Overweight/obesity
Lower calcium/magnesium intake	Lower physical activity/fitness
Lower diet quality (lower intake of fruits/vegetables, plant proteins, fiber)	Sleep disturbances (related to duration, quality, regularity, and/or disordered breathing)
Alcohol intake	Psychosocial stressors
	Air pollution

Secondary hypertension:

Causes (Disease / Syndrome)

➔ Diagnosed & Treated

➔ Marked improvement in HT + ↓CVD risk.

Secondary hypertension: 6 Causes

1. Kidney

1.1) Renal parenchyma: Glom.(Nephritis) / CKD (CGN, IgAN) ⭐

1.2) Polycystic kidney disease ⭐⭐

1.3) Renovascular disease: RAS (Atherosclerotic, FMD), Takayasu arteritis, PAN ⭐

Hematuria, Edema, Pulmonary edema, Abdominal discomfort, Drug induced AKI/HyperK, Extra-renal manifestation, Familial Hx., Resistant HT

2. Endocrine

2.1) Primary hyperaldosteronism: Adenoma, Bilat. Hyperplasia ⭐⭐⭐

2.2) Catecholamine secreting tumors: Pheochromocytoma, Paraganglioma

2.3) Cushing syndrome ⭐⭐⭐

2.4) Thyroid disorder: Hyper/Hypothyroidism

2.5) Rare: Hyperparathyroidism, Acromegaly, Renin secreting tumor

Resistant HT, HypoK, Weakness, Wt. gain/Loss, Paroxysmal HT, Palpitation, Clinical syndrome

Secondary hypertension: 6 Causes

3. Cardiovascular: Coarctation of aorta, TKA

Abnormal X-ray, Inter-limb blood pressure discrepancy, Neuro.def., Distal ischemia

4. OSA

Obesity, Resistant HT, Daytime sleepiness, Snoring/gasping during sleep

5. Drugs:

History, other adverse effect

NSAIDs, Glucocorticoids, CNIs, OCPs (mild HT), VEGF inhibitors, TKI, Nasal decongestant(Phenylephrine), Diet pills(phenylpropanolamine, sibutramine), Methylphenidate, chronic high dose paracetamol (4g/d)

Cocaine, Amphetamine

Exogenous mineralocorticoids, ESA, Anabolic steroids

Herbal remedies: ephedra/ma-huang

Lifestyle: Excessive alc. / Tobacco use, Heavy caffeine, High sodium intake, Black licorice root

Secondary hypertension: 6 Causes

6. **Genetics**

6.1 Genetic endocrine: MEN2A & B (Pheochromocytoma), NF-I (Essential HT, Pheochromocytoma, FMD>RAS), VHL (Pheochromocytoma, RCC, PKD)

6.2 Genetic nephrology: PKD (PKD1/2, Tuberous sclerosis TSC2), Glom. (Alport)

6.3 Monogenic Hypertension: GRA, AME, CAH, Liddle's syndrome, PHA type2 (Gordon syndrome), Geller

Familial History, Clinical syndrome

Secondary hypertension: Entry clues

- Secondary hypertension: 5%-25 % of all adult hypertension
- Most common: OSA (25%-50%)
- Primary aldosteronism (PA)
  - : 5%-10% of all hypertension
  - : **20% of resistant hypertension**
  - ⭐: **Spontaneous hypokalemia 20%-50%**
- Atherosclerotic renal artery disease
  - : 14%-40%
  - : Cause 2nd HT 0.1%-5%
- Resistant hypertension: OSA, PA, RVD, Pheo./Paragan., CKD ⭐

Common: ⭐
OSA (25-50%), **CKD** (14%), **PA** (5-25%), **Drug** (2-20%), **RVD** (0.1-5%)

Rare: Hypo/Hyperthyroidism (<1%), Pheo./Paragang. (<0.6%), Coarctation (0.1%), Cushing (<0.1%), PHPT (rare), Acromegaly (rare), other mineralocorticoid excess (rare)

Secondary hypertension: Entry clues

Does the patient have any of the following conditions associated with secondary HTN?

- Drug-resistant/induced HTN — **Resistant HT**
- Abrupt onset of HTN
- Onset of HTN at <30 y (<40 y) — **Previous Hx**
- Exacerbation of previously controlled HTN — **Previous Hx**
- Disproportionate TOD for degree of HTN — **PE**
- Accelerated/malignant HTN — **PE**
- Onset of diastolic HTN in older adults (age ≥65 y) — **Late onset**

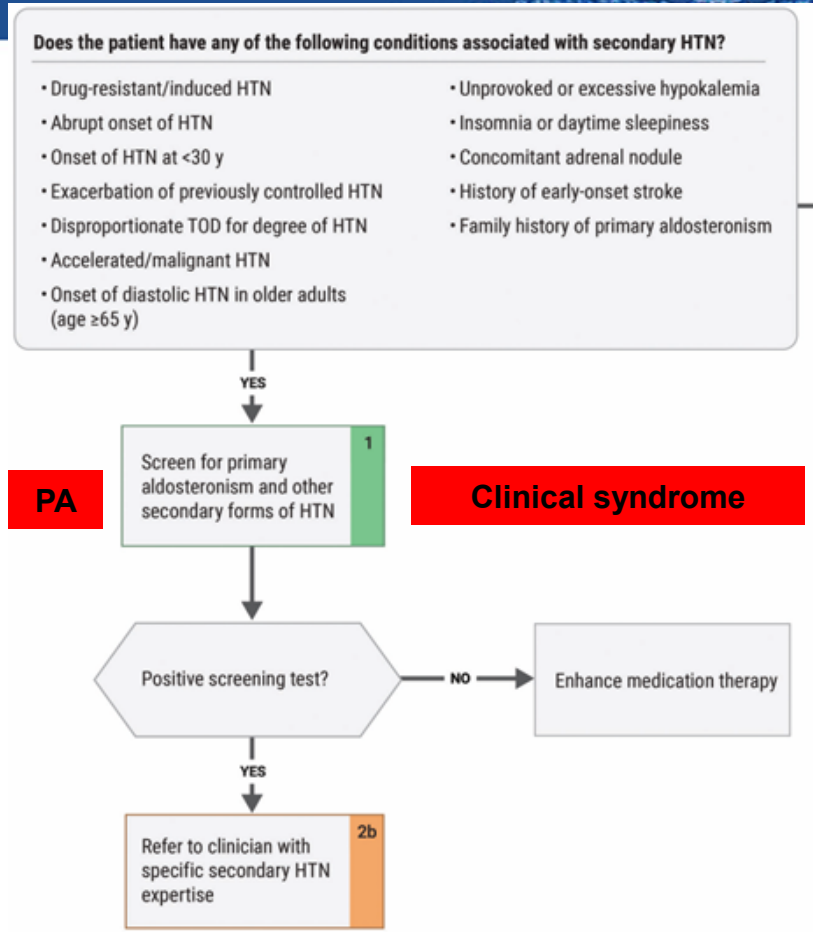
Character of HT

- Unprovoked or excessive hypokalemia
- Insomnia or daytime sleepiness
- Concomitant adrenal nodule — **PA**
- History of early-onset stroke
- Family history of primary aldosteronism

Clinical syndrome

Cushing, Nephritis, PKD, RVD, Coarct./TKA

Secondary hypertension: Entry clues



มาด้วยอาการอื่น:
ปวดศีรษะ, ปวดเมื่อยกล้ามเนื้อ อ่อนแรง, Target organ damage, Clinical syndrome

HT structure
➔ อาการไม่ชัดเจน approachไม่ได้
➔ ไม่แน่ใจClinical syndrome / หาโครงพูด

Secondary hypertension: Approach

1. **Clues to secondary HT**
    1.1) Character of HT
    1.2) Clinical setting / syndrome
2. **DDx cause: Clinical**
3. **Review of systems/PE, target organ damage, co-morbidity, drugs**
4. **Investigation**

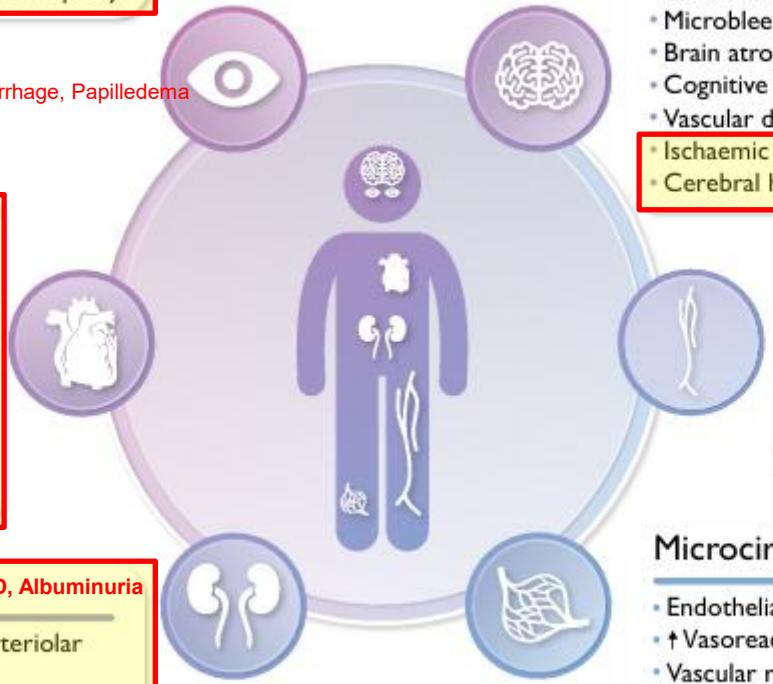
TOD / HMOD

Eye
- Microvascular remodelling
- Hypertensive retinopathy

Gr.1&2: Copper wire, AV nicking
➔ Long duration
Gr.3&4: Cotton wool spots, Hemorrhage, Papilledema
➔ ACC. HT

Brain
- White matter lesions
- Silent microinfarcts
- Microbleeds
- Brain atrophy
- Cognitive impairment
- Vascular dementia
- Ischaemic stroke
- Cerebral haemorrhage

Heart
- LVH
- LA and LV dilatation
- AF
- Obstructive and non-obstructive CAD
- Myocardial Infarction
- Diastolic and/or systolic heart failure



Large and medium arteries
- Atherosclerosis **PAD**
- Vascular calcification
- Arterial stiffness

Kidney **CKD, Albuminuria**
- Glomerular arteriolar hypertension
- Glomerulosclerosis
- Albuminuria/Proteinuria
- ↓GFR

Microcirculation
- Endothelial dysfunction
- ↑Vasoreactivity
- Vascular remodelling
- Fibrosis and inflammation
- ↑Peripheral vascular resistance

See footnote for information on sex-differences

ESC

History and symptoms suggesting HMOD, established CVD, and renal disease

Brain and eyes: syncope, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization, cognitive impairment, dementia.

Heart: chest pain, shortness of breath, oedema, myocardial infarction, coronary revascularization, history of palpitations, arrhythmias (especially AF), heart failure.

Kidneys: polyuria, nocturia, haematuria, urinary tract infections, patient or family history of CKD (e.g. polycystic kidney disease).

Peripheral arteries: cold extremities, intermittent claudication, leg ulcers, peripheral revascularization.

TOD / HMOD:
History & Physical examination

Signs of HMOD or established CVD

Neurological examination and cognitive status (based on clinical suspicion).[211] **Eye ground**

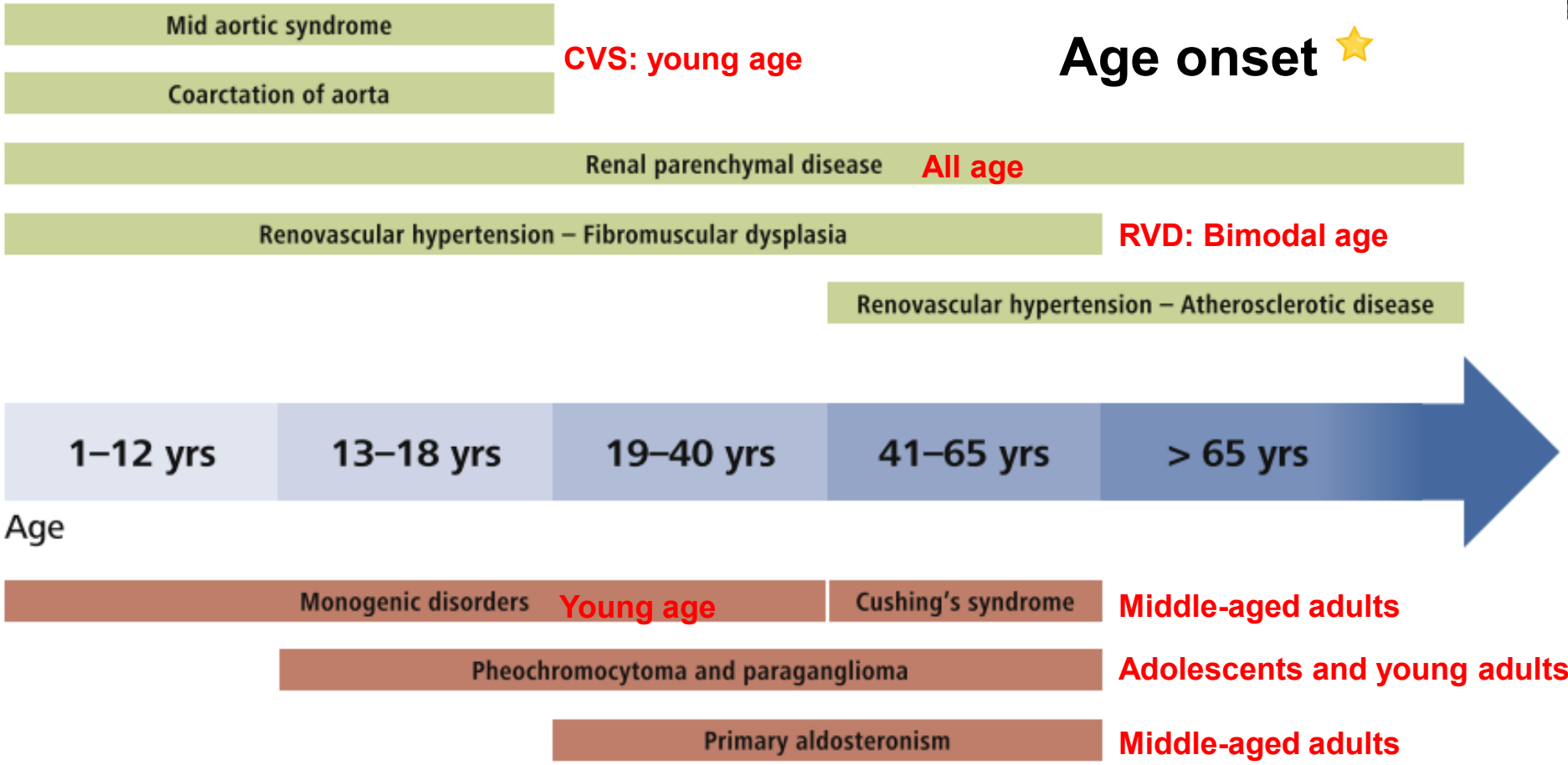
Palpation and auscultation of heart and carotid arteries.

Auscultation of abdominal aorta, iliac, and femoral arteries.

Palpation of peripheral arteries.

Comparison of BP in both arms (at least once).

Secondary hypertension: DDx



Age group	Per cent with underlying cause	Typical causes
Young children (<12 years)	70 - 85	• Renal parenchymal disease • Coarctation of the aorta • Monogenic disorders
Adolescents (12–18 years)	10–15	• Renal parenchymal disease • Coarctation of the aorta • Monogenic disorders
Young adults (19–40 years)	5–10	• Renal parenchymal disease • Fibromuscular dysplasia (especially in women) • Undiagnosed monogenic disorders
Middle-aged adults (41–65 years)	5–15	• Primary aldosteronism • Obstructive sleep apnoea • Cushing's syndrome • Phaeochromocytoma • Renal parenchymal disease • Atherosclerotic renovascular disease
Older adults (>65 years)	5–10	• Atherosclerotic renovascular disease • Renal parenchymal disease • Thyroid disease

Secondary hypertension: DDx

Primary aldosteronism ⭐

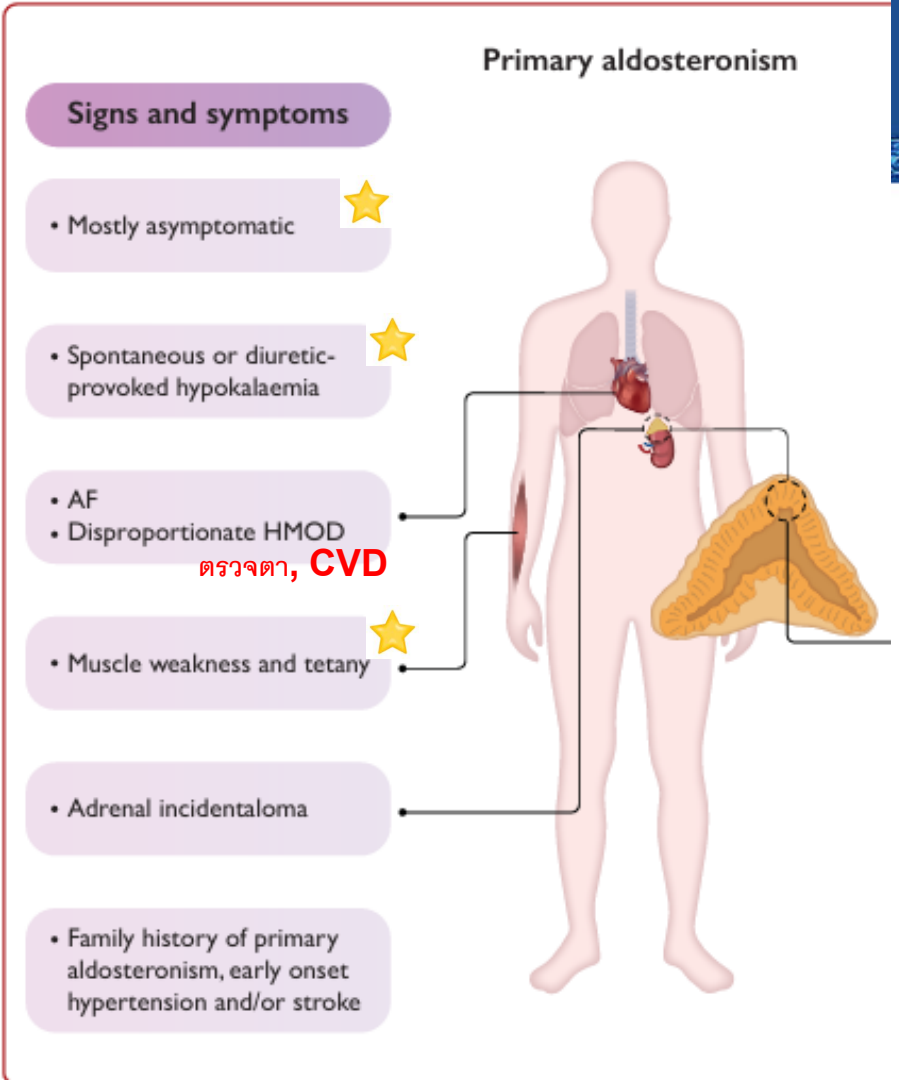
- Resistant HT
- HT + OSA

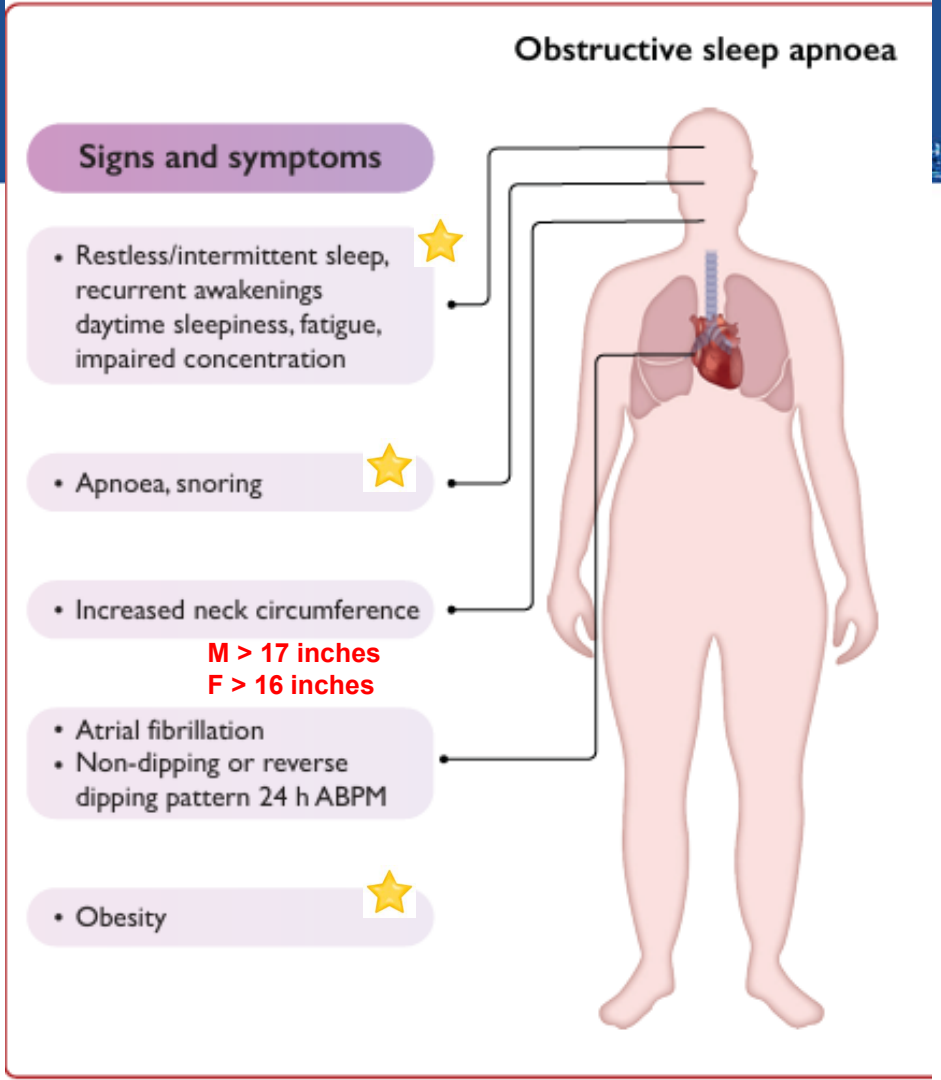
Screening

- Electrolyte, Kidney function, Renal K loss
- PAC, PAC/PRA (correct K + withdrawal MRA 4-6 week)

Confirmatory test

- Saline loading test
- Adrenal CT scan
- AVS





Secondary hypertension: DDx

Obstructive sleep apnea

- Resistant HT
- STOP-Bang
- AF

Test

- Polysomnography

Secondary hypertension: DDx

AD Polycystic kidney disease ⭐

- HT (50-70% prior GFR decline) onset 30 y
- Nocturia, polyuria
- **Abdominal or flank pain / Abdominal mass** ⭐
- Gross hematuria
- Recurrent UTI, Nephrolithiasis
- CKD / ESKD
- Hepatomegaly, MVP, ICA
- Familial history ⭐

>40-45 y

Test

- Kidney function, UA
- Imaging
- Gene

CKD (CGN)

- HT in the young
- **Edema**
- CKD
- Hematuria / Foamy urine
- (Extra renal manifestation)

Test

- Kidney function, UA
- Serology
- Pathology

Bimanual palpation

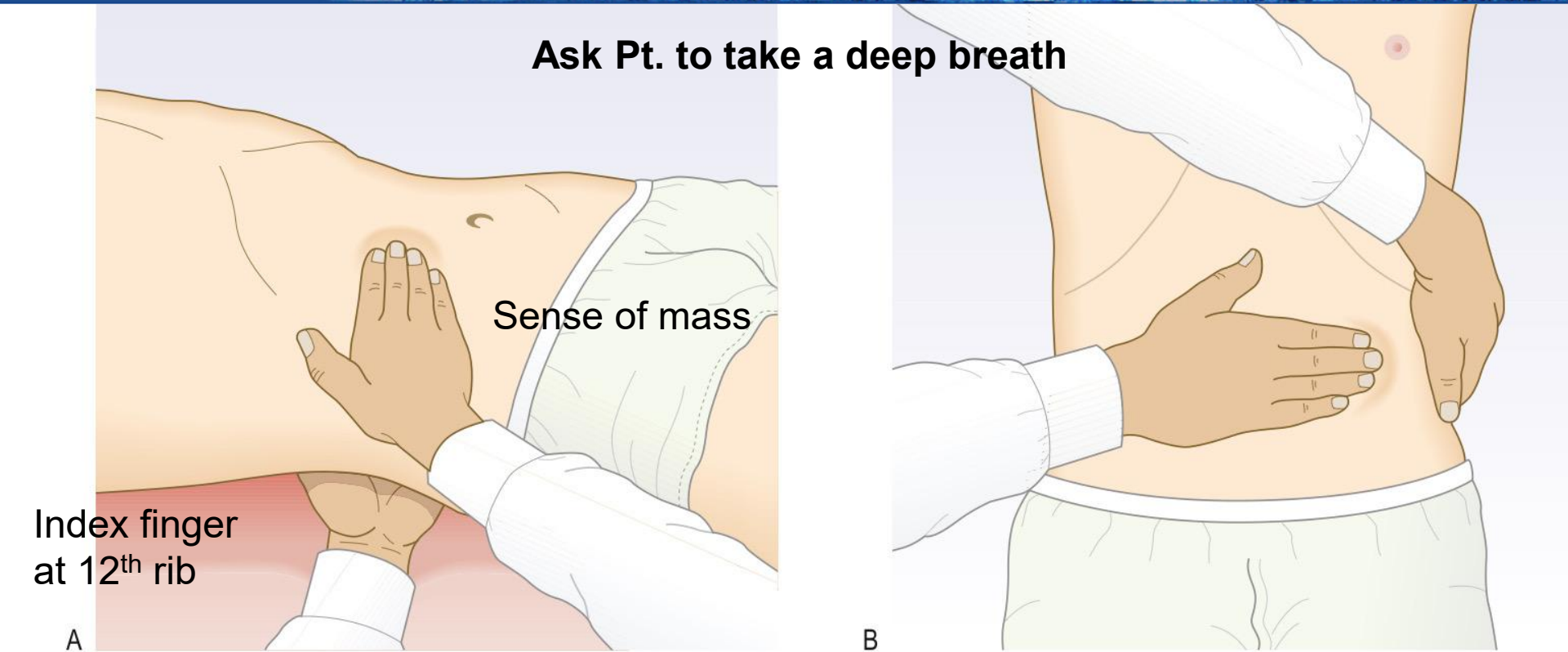
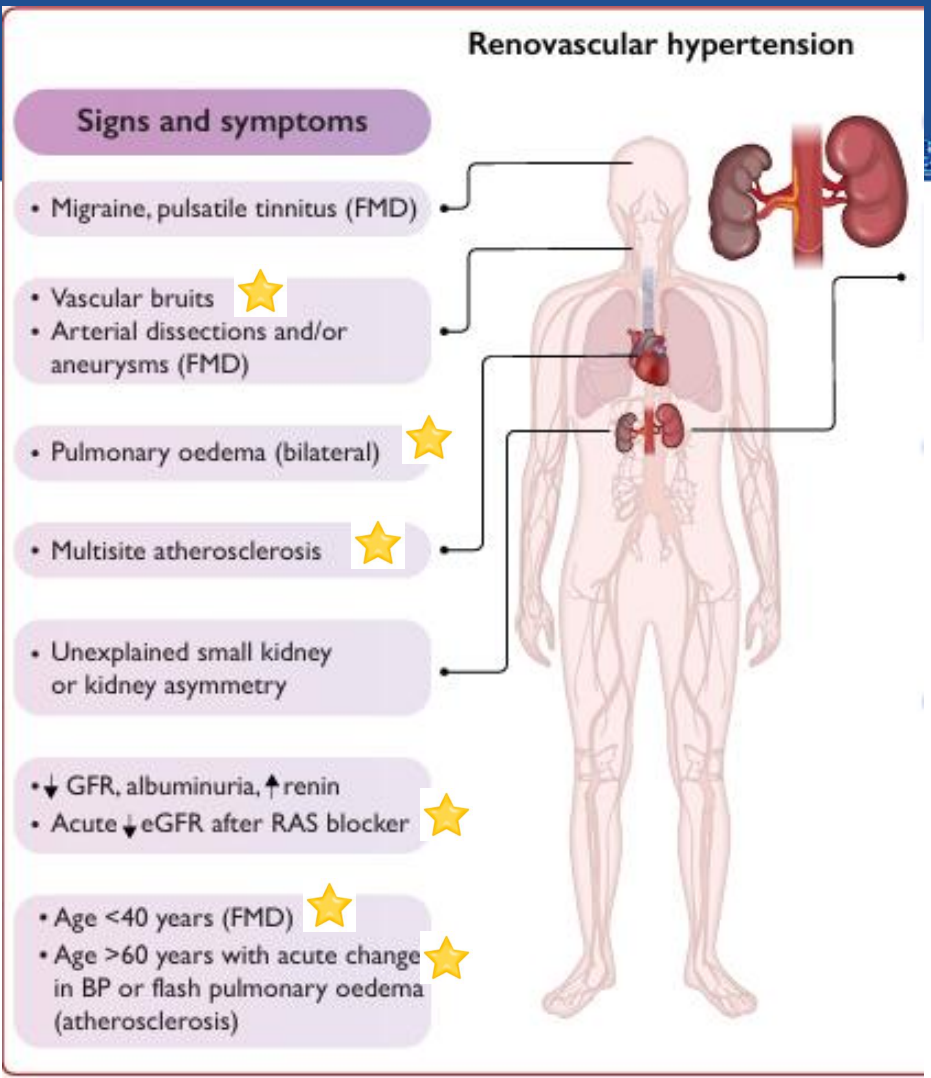


Fig. 12.12 Palpation of the kidney. A Right kidney. B Left kidney.

Get above mass at flank

Secondary hypertension: DDx



Renovascular hypertension

- Resistant HT
- Abrupt onset, worsening to control
- Sudden / unexplained pulmonary edema ★

Screening

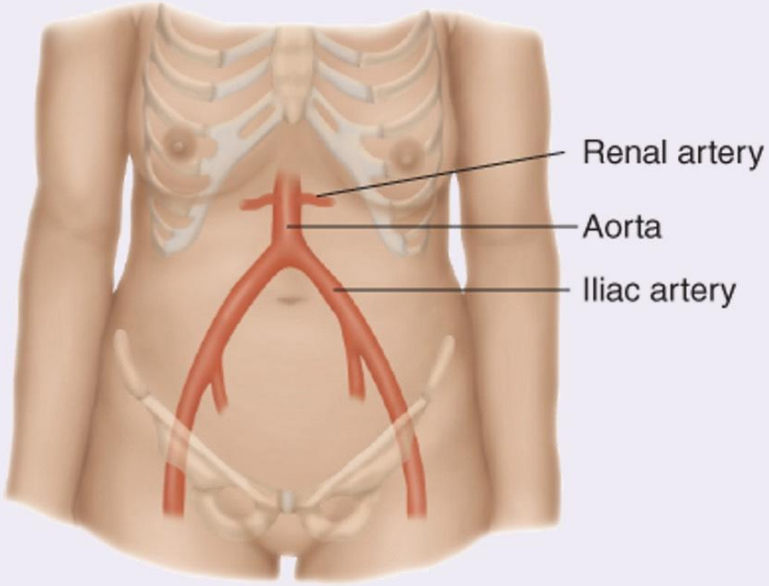
- Electrolyte, Kidney function
- US kidney / US doppler
- MRA, CT arteriography

Confirmatory test

- Angiography

Abdominal bruit

- **Supine position**
- **Location: all four quadrants**
- **Renal artery:** epigastrium, costal margin, above umbilicus lateral to midline, (flank / CVA)



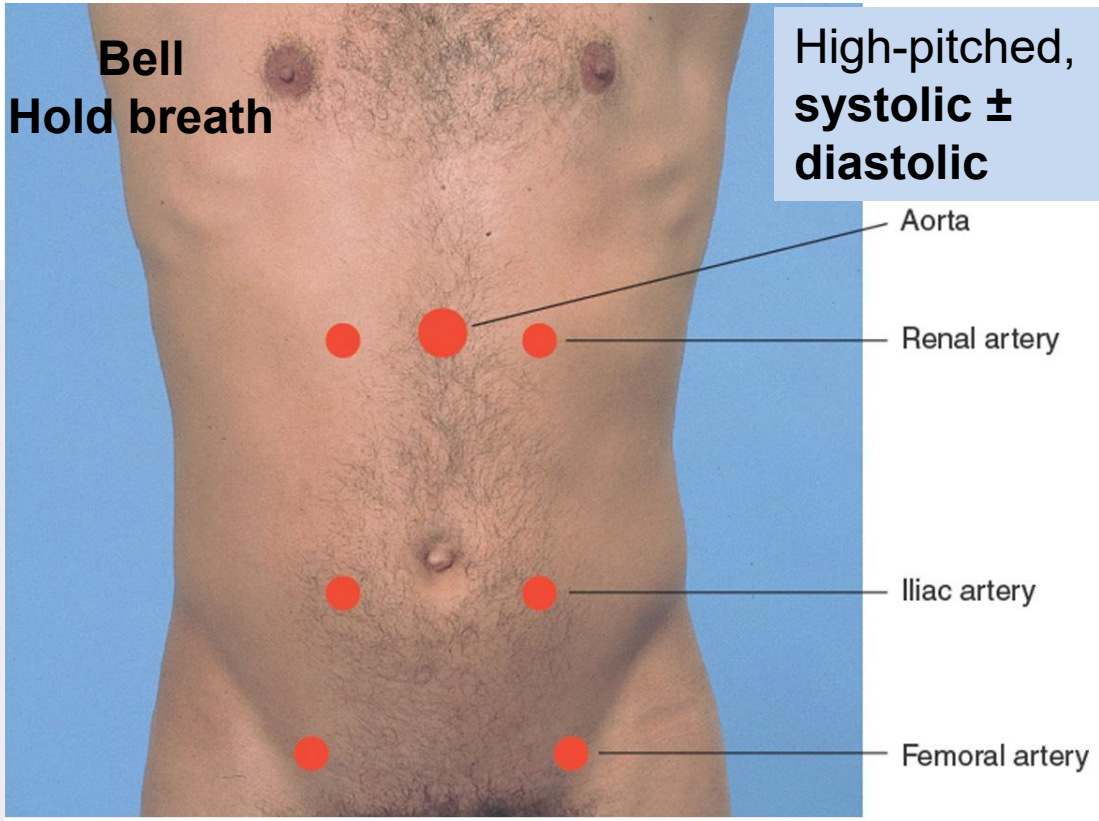


FIGURE 19-11. Abdominal auscultatory areas for bruits.

Secondary hypertension: DDx

Renovascular hypertension

Takayasu arteritis

≥5

ABSOLUTE REQUIREMENTS		
	Age ≤ 60 years at time of diagnosis **20-30 y**	
	Evidence of vasculitis on imaging[1]	
ADDITIONAL CLINICAL CRITERIA		
★	Female sex	+1
	Angina or ischemic cardiac pain	+2
★	Arm or leg claudication	+2
★	Vascular bruit[2]	+2
★	Reduced pulse in upper extremity[3]	+2
	Carotid artery abnormality[4]	+2
★	Systolic blood pressure difference in arms ≥ 20 mm Hg	+1
ADDITIONAL IMAGING CRITERIA		
	Number of affected arterial territories (select one)[5]	
	One arterial territory	+1
	Two arterial territories	+2
	Three or more arterial territories	+3
	Symmetric involvement of paired arteries[6]	+1
	Abdominal aorta involvement with renal or mesenteric involvement[7]	+3

Polyarteritis nodosa

Male>Female / 40-60

1990 criteria for the classification of polyarteritis nodosa

★ **1. Weight loss >4 kg**
Loss of 4 kg or more of body weight since illness began. not due to dieting or other factors

★ **2. Livedo reticularis**
Mottled reticular pattern over the skin of portions of the extremities or torso

3. Testicular pain or tenderness
Pain or tenderness of the testicles, not due to infection, trauma, or other causes

4. Myalgias, weakness, or leg tenderness
Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness

★ **5. Mononeuropathy or polyneuropathy**
Development of mononeuropathy. multiple mononeuropathies, or polyneuropathy

6. Diastolic BP >90 mm Hg
Development of hypertension with the diastolic BP higher than 90 mm Hg

7. Elevated BUN or creatinine
Elevation of BUN >40 mg/dl or creatinine >1.5 mg/dl, not due to dehydration or

★ **8. Hepatitis B virus**
Presence of hepatitis B surface antigen or antibody in serum

9. Arteriographic abnormality
Arteriogram showing aneurysms or occlusions of the visceral arteries not due to obstruction of leg muscles, arteriosclerosis. fibromuscular dysplasia, or other noninflammatory causes

10. Biopsy of small or medium-sized artery showing PMN

Histologic changes showing the presence of granulocytes or granulocytes and mononuclear leukocytes in the artery wall

Secondary hypertension: DDx

Aortic coarctation

- Young adult with HT (age<30y)
- BP higher in upper extremities than lower
- Absent femoral pulse
- Continuous murmur over back/chest
- Abdominal bruit

Test

- CXR: Figure of 3 sign / Inferior rib notching (Roesler sign)
- Echo.
- CT angiogram/MRA

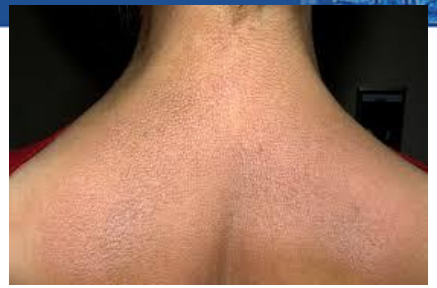
Cushing ⭐

- Rapid wt. gain
- Proximal muscle weakness
- Hyperglycemia
- Easily bruising
- Violaceous striae
- Hirsutism
- Dorsal/supraclav. fat pad
- Central obesity, moon face
- Facial plethora

Pheochromocytoma /Paraganglioma ⭐

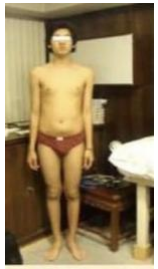
- Resistant HT
- Orthostatic HT
- Paroxysmal
- Spell, BP lability
- Headache, sweating. Palpitation, piloerection
- Adrenal incidentaloma
- Familial history
- ⭐ Syndrome: e.g., Skin: café-au-lait spot, neurofibromatosis / MEN2 / VHL

Pheochromocytoma/Paraganglioma

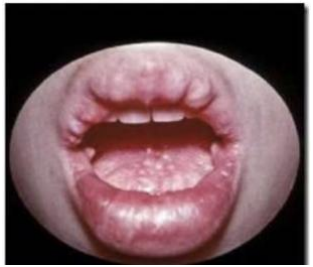


Cutaneous lichen amyloidosis

Med PA Phe / MEN-2A / RET gene



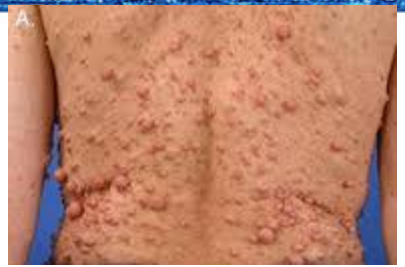
Marfanoid



Mucosal neuromas

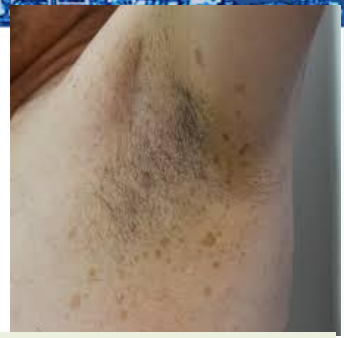
Med Phe Mu Ma / MEN-2B / RET gene

Café-au-lait macules

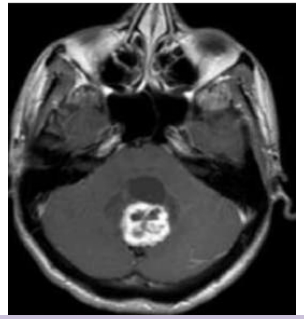


Neurofibroma

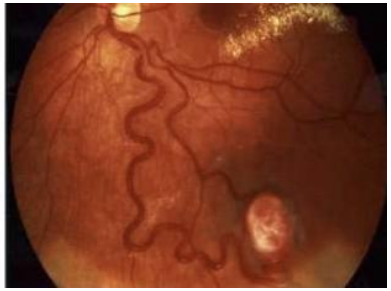
Neurofibromatosis / NF-1 gene ⭐



Axillary/lng. skin fold freckling



Cerebellar hemangioblastoma



Retinal hemangioblastoma

Von-Hippel-Lindau
VHL gene

HT + Hypokalemia with renal K loss

PAC / PRA

PRA ↑ PAC ↑
PAC/PRA=10

PRA ↓ PAC ↑
PAC/PRA≥20
PAC≥15 ng/dL

PRA ↓ PAC ↓

PA: 28%
RVD: 13%
Cushing: 6%
➔ Drug: 44%

-Reno-vascular HT (RAS, Coarctation of aorta)
-Renin secreting tumor (RCC, Wilm's tumor)
-Malignant HT
-Diuretic use?

-Primary aldosteronism
-Glucocorticoid remediable aldosteronism (GRA)
-Ectopic aldosterone secreting tumor

Adrenal adenoma: young <50y., more woman, more severe HT, more severe hypoK, solitary adrenal tumor

Adrenal hyperplasia: older than adenoma, more men, less severe HT/hypoK, normal or bilateral adrenal gland enlargement

GRA: Familial hyperaldosteronism type I, AD, strong familial Hx of HT/early onset HT/ early CVD in family / refractory HT, Chimeric gene of CYP11B1(11-OHase gene on ch.8q) & CYP11B2 (Aldosterone synthase gene)>>Aldosterone synthase is inappropriately regulated by ACTH, Test: Genetic test, U 18-OHcortisol, Dexamethasone suppression test > Treatment (FH typeอื่นใช้ MR antagonist)

-Cushing's syndrome
-Congenital adrenal hyperplasia (CAH)
(11B or 17a -hydroxylase def.)
-Liddle syndrome
-Apparent mineralocorticoid excess (AME)
-Acquired AME (Licorice, Posaconazole, Itraconazole, Grapefruit, Carbenoxolone>Tx peptic ulcer, Obstructive jaundice)
-Geller syndrome
-DOC producing tumor
-Ectopic ACTH, Ectopic mineralocorticoid (Fludrocortisone, Abiraterone)

Normal cortisol

Liddle: AD, Pseudo hyperaldosteronism type1, SCMM1a 1B 1G, gain of function mutation of ENaC of B or Y, HT in the young, growth retardation, polyuria, Tx: ENaC blocker(amiloride, triamterene) *not response to MR blocker

Normal cortisol

AME: AR, defect in 11B-HSD-2, increase T1/2 of intracellular cortisol of principal cell, HT in the young, growth retardation, low BW, polyuria, Dx: U free cortisol/free cortisone ratio>10, Tx: MR blocker, ENaC blocker

Licorice: Glycyrrhetinic acid > inhibit 11B HSD2 > Acquired AME

High cortisol

Cushing: excess of cortisol over 11B-HSD-2

Geller: AD, agonist effect of progesterone on mutated MR, HT & HypoK in pregnancy, Dx: test NR3C2 mutation, Tx: improve after delivery, ENaC blocker, **X MR blocker (exacerbate this condition)

Normal cortisol

CAH: 11B OH def. = cyp11B1, post-natal virilization / 17a OH def. = cyp17A1, adulthood, sex steroid def., Tx: GCs, MR blocker prefer in 17a OH def.

Abiraterone: inh. 17a OH&C17,20-lyse > increased deoxycorticosterone > cortisol like activity, Tx: GCs or MRA blocker

Low cortisol

Key!!: Intra-cellular Principal cell > 11B hydroxysteroid dehydroxygenase (11B HSD2) for conversion of cortisol to cortisone (Inactive)

...MR equivalent affinity for ald.& cortisol

...11BHSD2 > inhibit cortisol stimulating MR

Medications/ Substances

Nonprescription drugs/substance
Alcohol
Caffeine[28]
Decongestants (eg, phenylephrine, pseudoephedrine)
Herbal supplements (eg, Ma Huang, ephedra, St. John's wort [with MAO inhibitors, yohimbine])
Black licorice[29]
NSAIDs; acetaminophen
Recreational drugs (eg, "bath salts" [MDPV], cocaine, methamphetamine, etc)

Prescription drugs
Sudden withdrawal of central-acting sympatholytic drugs such as clonidine and tizanidine
Amphetamines† (eg, amphetamine, methylphenidate dexmethylphenidate, dexamfetamine, lisdexamfetamine, dextroamphetamine)
Antidepressants† (eg, MAOIs, SNRIs, TCAs)
Atypical antipsychotics† (eg, risperidone, olanzapine)[33,34]
Immunosuppressants† (eg, cyclosporine)
Oral contraceptives†
Systemic corticosteroids† (eg, dexamethasone, fludrocortisone. methylprednisolone, prednisone, prednisolone)
Angiogenesis inhibitor† (eg, bevacizumab) and tyrosine kinase inhibitors (eg, sunitinib, sorafenib)
Androgen deprivation therapy† such as CYP 17 inhibitors (eg, abiraterone, orteronel) or androgen receptor antagonist (eg, enzalutamide)[36]

Secondary hypertension: Approach

1. **Clues to secondary HT**
   - 1.1) Character of HT
   - 1.2) Clinical setting / syndrome
2. **DDx: Clinical**
   - **2.1) Endocrine HT**
     - ➔ DDx แม้ไม่มี Clues: PA, Pheo.
     - ➔ มีClinical clues: Cushing, Thyroid, Acromegaly, Pheo.
     - ➔ Genetic endocrine “esp. Pheochromocytoma”
   - **2.2) HT + Hypokalemia (**ถ้าซักประวัติได้**)** ➔ PAC / PRA
   - **2.3) Kidney disease** ➔ RVD / PKD / Glom.
   - **2.4)** อื่น ๆ เช่น **CVS /** ยา / Monogenic HT: AME / Gordon / Liddle
3. **Review of systems/PE, target organ damage, co-morbidity, drugs**
4. **Investigation**

Secondary hypertension: Review

Risk factors

Family and personal history of hypertension, CVD, or renal disease.
Family and personal history of associated CVD risk factors.
Smoking history (including vaping).
Dietary history (including but not exclusive to salt intake).
Alcohol consumption.
Physical activity/sedentary lifestyle.
History of erectile dysfunction.
Migraine with aura.
Autoimmune inflammatory diseases.
Human immunodeficiency virus.
Sleep history, snoring, sleep apnoea.
Psychosocial factors (chronic stress, depression, social deprivation, low socio-economic status, discrimination, gender-based violence).
Previous hypertension in pregnancy/pre-eclampsia and other pregnancy-related complications (gestational diabetes, miscarriage/stillbirth, pre-term labour).
Early menopause, polycystic ovary disease.

Medication history

Current/past BP-lowering medication including effectiveness and intolerance and adverse events with previous medications.
Adherence to and persistence with prior and current treatments.
Use of drugs or substances that may increase BP.

Anthropometric measures ⭐

Weight and height for BMI calculation.
Waist circumference.

Signs of secondary hypertension

⭐ Skin inspection: cafe-au-lait patches of neurofibromatosis (phaeochromocytoma/paraganglioma).
⭐ Kidney palpation for signs of renal enlargement (polycystic kidney disease).
Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension.
⭐ Comparison of radial with femoral pulse, inter-arm BP difference in young individuals with aortic coarctation (aortic murmur may also be heard).
⭐ Signs of Cushing's disease or acromegaly.
⭐ Signs of thyroid or parathyroid disease.
⭐ Neck circumference of >40 cm in men, >35 cm in women (OSAS).

Case 1

- **A 39-year-old woman presented with intermittent scalp tightness for 6 years.**
  “ปวดตึงศีรษะมา 6 ปี”

- The pain was mild, dull, and episodic, lasting less than 30 minutes and resolving spontaneously.
- She denied weakness, numbness, speech difficulty, visual or hearing changes, dizziness, or gait instability.
- 2 years ago, she also reports intermittent bilateral thigh muscle pain and episodic proximal thigh weakness lasting 7–8 hours, which improves with analgesics.

- **Physical exam.:** BP 170/100 mmHg, BMI 29 kg/m2, CVS/RS/Neuro. system WNL

Further Hx & PE ?
How to approach ?

Renovascular hypertension

Causes

1. Atherosclerotic RAS (ARAS)
2. Fibromuscular disease (FMD)
3. Extrinsic fibrous band
4. Renal trauma (Dissection/Page kidney/Segmental renal infarction)
5. Aortic dissection, Arterial embolus
6. Miscellaneous: malignancy, hypercoagulable stage

ARAS	FMD
Men & Woman	Woman
Age>50 y, older age	<40 y (mean 52 y)
Atherosclerotic disease	absent
Location: Proximal third	Middle to distal third
Irregular vessel wall	String of beads
Nearly total occlusion	Rare total occlusion
Ischemic atrophy	Rare in ischemia
Medication +/- angioplasty	Angioplasty

Renovascular hypertension

Unilateral Renal Artery Stenosis

RAAS ↑↑

Pressure natriuresis

Reduced renal perfusion

↑ Renin–angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone

Angiotensin II dependent hypertension

Increased renal perfusion

Suppressed RAS

Increased Na^+ excretion (pressure natriuresis)

X flash pulmonary edema

Effect of blockade of RAS
Reduced arterial pressure
Enhanced lateralization of diagnostic tests
Glomerular filtration rate (GFR) in stenotic kidney may fall

Response RAASi ↑↑

Diagnostic tests
Plasma renin activity elevated
Lateralized features, e.g., renin levels in renal veins, captopril-enhanced renography

A

Bilateral Renal Artery Stenosis

RAAS ↑

Bilateral

Stenosis of solitary kidney

Reduced renal perfusion

↑ Renin–angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone

Normal or low angiotensin II

Inhibit RAS

Impaired Na^+ and water excretion

Volume expansion

Increased arterial pressure

flash pulmonary edema

Effect of blockade of RAS
Reduced arterial pressure only after volume depletion
May lower GFR

Response RAASi ↑

Diagnostic tests
Plasma renin activity normal or low
Lateralized features: none

B

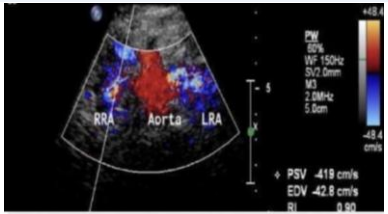
Investigation

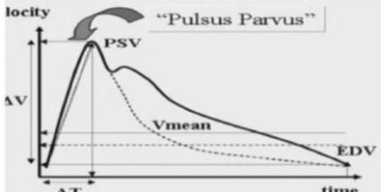
Renovascular hypertension

Table 1. Summary of Imaging Modalities Used to Diagnose Atherosclerotic Renovascular Disease

Imaging Modality	Sensitivity	Specificity	Strengths	Limitations
Duplex ultrasound	91%-100%	82%-91%	Inexpensive, noninvasive, provides waveform and velocity data, provides data about kidney viability (resistive index)	Operator-dependent, limited by high BMI, limited availability in some countries
Multidetector CTA	64%-96%	90%-92%	Rapid multiplanar acquisition, allows detection of accessory renal arteries	Low/moderate levels of radiation, requires iodinated contrast
MRA	94%-97%	85%-93%	No radiation or iodinated contrast required	Long acquisition times (~1 h), may overestimate degree of stenosis
Catheter angiography	100%	100%	Gold standard of renal artery evaluation, enables measurement of pre- and postintervention gradients, can evaluate and treat in same setting	Invasive procedure, only 2D planar images acquired, ideally requires iodinated contrast (CO_2 can be substituted with lesser resolution)

Recommendations	Class	Level
DUS (as first-line), CTA and MRA are recommended imaging modalities to establish a diagnosis of RAD.	I	B
DSA may be considered to confirm a diagnosis of RAD when clinical suspicion is high and the results of non-invasive examinations are inconclusive.	IIB	C
Renal scintigraphy, plasma renin measurements before and after ACEI provocation and vein renin measurements are not recommended for screening of atherosclerotic RAD	III	C





Doppler US

PSV > 180 cm/s

RAR > 3.5

Management

Renovascular hypertension

Recommendations for Renal Artery Stenosis
References that support recommendations are summarized in the Evidence Table.

COR	LOE	Recommendations
1	A	1. In adults with hypertension and atherosclerotic renal artery stenosis, medical therapy is recommended to reduce kidney and CVD morbidity and mortality.[1–3]
2a	C-EO	2. In adults with hypertension and atherosclerotic renal artery stenosis for whom medical management has failed (eg, resistant hypertension, worsening kidney function, and/or acute HF), it is reasonable to refer patients for revascularization by percutaneous renal artery angioplasty and/or stent placement.
2b	C-LD	3. In adults with hypertension and nonatherosclerotic renal artery stenosis, including fibromuscular dysplasia, it may be reasonable to refer patients for revascularization by percutaneous renal artery angioplasty.[4]

Goal of therapy: blood pressure & volume control, preservation of renal function and cardiovascular risk reduction.

Strategy of therapy composed of medical therapy with/without revascularization.

ARAS ➔ Medication

FMD ➔ Percutaneous renal artery angiography

Revascularization in ARAS ➔ Fail medication with symptom

AHA/ACC 2025
ESC 2024

Management

Renovascular hypertension

Recommendation	Class	Level
ACEIs/ARBs are recommended for treatment of hypertension associated with **unilateral RAS.** ★	I	B
Calcium channel blockers, beta- blockers and **diuretics** are recommended for treatment of hypertension associated with renal artery disease.	I	C
ACEIs/ARBs may be considered in **bilateral severe RAS** and in the case of stenosis in a **single functioning kidney**, if well- tolerated and under close monitoring. ★	IIb	B

ESC/ESH 2018

Smoking cessation is recommended in all patients with PADs.	I	B
A healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs.	I	A
Recommended to reduce LDL-C to < 70 mg/dL or decrease it by ≥ 50% if baseline 70–135 mg/dL.	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs.	I	C
In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg.	I	A

ESC/ESH 2018

Management

Renovascular hypertension

Recommendations	FMD	Class[a]	Level[b]
Renal artery angioplasty without stenting should be considered for patients with hypertension and haemodynamically significant renal artery stenosis due to fibromuscular dysplasia.[941]		IIa	C

Women of childbearing age with RA aneurysms should be treated before pursuing pregnancy because of the risk for rupture during pregnancy or delivery.

Other recommended treatments for patients with FMD are antiplatelet agents and smoking cessation.

ESC 2024

Management

Renovascular hypertension

Recommendations	Class[a]	Level[b]
Renal artery angioplasty and stenting may be considered in patients with haemodynamically significant, atherosclerotic, renal artery stenosis (stenosis of 70%–99%, or 50%–69% with post-stenotic dilatation and/or significant trans-stenotic pressure gradient) with:	IIb	C
★ Recurrent heart failure, unstable angina, or sudden onset flash pulmonary oedema despite maximally tolerated medical therapy;		
★ Resistant hypertension;		
★ Hypertension with unexplained unilaterally small kidney or CKD;		
★ Bilateral renal artery stenosis or unilateral renal artery stenosis in a solitary viable kidney.[942,943]		

Atherosclerotic RAS
"Revascularization"

ESC 2024

In patients with an indication to renal artery revascularization and technically unfeasible, or failed, renal artery angioplasty and stenting, open surgical revascularization may be considered.	IIb	C
Renal artery angioplasty is not recommended in patients without confirmed haemodynamically significant renal artery stenosis.[c] [938,939]	III	A

ESC 2024

Management

Renovascular hypertension

Definite indications

- Acute pulmonary edema or acute decompensations of heart failure and high-grade RAS[96]
- Progressive CKD in high-grade (>75%) RAS (bilateral or solitary kidney)[21]
- AKI due to acute renal artery occlusion or high-grade RAS[83]
- ACEi or ARB intolerance in high-grade RAS
- Kidney transplant with RAS (symptomatic or asymptomatic)[91]

Possible indications

- Chronic heart failure and high-grade RAS[31,73]
- Coexistence of progressive CKD and uncontrolled hypertension[21,84]
- Asymptomatic high-grade RAS (either bilateral or supplying solitary kidney) with viable renal parenchyma (to prevent atrophy)
- New (<3 mo) dialysis patient with nonfunctioning but possibly viable kidney[53-55,83,84]

Nonindications

- Moderate to severe hypertension alone
- Asymptomatic unilateral or bilateral (<75%) RAS[63,70,71]

Atherosclerotic RAS

"Revascularization"

KDIGO 2022

Table 3. Features of Renal Parenchymal Viability or Nonviability in Atherosclerotic Renovascular Disease

Sign	Potentially Viable	More Likely Nonviable
Timing of kidney function deterioration, mo	<6	≥6
Proteinuria	UACR <200 mg/g (20 mg/mmol)	UACR >300 mg/g (30 mg/mmol) or UPCR >500 mg/g[a] (50 mg/mmol)
Cortical thickness	Cortex distinct (eg, >0.5 cm depth)	Loss of corticomedullary differentiation; no cortex
Renal resistive index	<0.8	>0.8
Renal artery length, cm	>8[b]	<7

Case 2

- **A 65-year-old man presented with worsening BP control over last 2 months** “ความดันโลหิตคุมได้แย่ลง ในช่วง 2 ปี”

- Underlying diseases: T2DM, HT, CAD, CKD G3, PAD
- His BP are now consistently above 150/90 mmHg with bilateral pitting edema. Current treatment: “ยาความดัน 4 ชนิด ยาขับปัสสาวะ 1 ชนิด”
- Two months ago: progression of CKD from G3 to G4. “หลังปรับเพิ่มยาความดัน”

- **Physical exam.:** BP 160/90 mmHg (all ext.), CVS/RS/Neuro. system WNL

Eye exam.? **Further PE ?**
Resistant HT ? **How to approach ?**

Eye ground: copper wire / AV nicking

Cotton wool

Resistant hypertension

Confirm treatment resistance with 1 of the following:

- Office BP ≥130/80 mm Hg and on ≥3 antihypertensives
  - Combination of ACEi or ARB + CCB + thiazide-like diuretics preferred
- Office BP <130/80 mm Hg but requires ≥4 antihypertensives
  - Combination of ACEi or ARB + CCB + thiazide-like diuretics preferred

- These ESC Guidelines do not include the terms 'controlled resistant hypertension' (BP at target but requiring ≥4 medications) or 'refractory hypertension' (BP not at target despite ≥5 medications).

<140 mmHg and/or <90 mmHg, respectively. These uncontrolled BP values must be confirmed by out-of-office BP measurements (HBPM or ABPM—

Exclude pseudoresistance ★

- Ensure accurate office BP measurements
- Assess for medication nonadherence with prescribed regimen
- Obtain home, work, or ambulatory BP readings to exclude white-coat effect

Identify and reverse contributing lifestyle factors* ★

Causes of resistant hypertension
Behavioural factors
Overweight/obesity
Physical inactivity
Excess daily dietary sodium
Excess habitual alcohol consumption

Discontinue or minimize interfering substances† ★

AHA/ACC 2025
ESC 2024

Resistant hypertension

Screen for secondary causes of hypertension‡ ⭐

Pharmacological treatment ⭐

- Maximize diuretic therapy
  - Replace thiazide-type diuretics with chlorthalidone 12.5-25 mg qd or indapamide 1.25-2.5 mg qd
- Add spironolactone (25-50 mg qd) or equivalent dosage of eplerenone (25-50 mg BID) if eGFR ≥45
- Use chlorthalidone or loop diuretics in patients with CKD stage 4 or greater
- Add agents with different MOA
  - BB, central sympatholytic drugs, or nondihydropyridine CCB for elevated heart rate
- Add dual endothelin-receptor antagonist (ERA) or potent vasodilators
  - Dual ERA, eg, aprocitentan, or direct vasodilator eg, hydralazine or minoxidil (only if already on BB [or bradycardic] and loop diuretic)

Refer to specialist:

- For known or suspected secondary cause(s) of hypertension
- If BP remains uncontrolled >6 months of treatment

AHA/ACC 2025
ESC 2024

Case 3

- **A 40-year-old man presented with hypertension** “ตรวจพบความดันโลหิตสูง”

- **7 years ago**, he was diagnosed with hypertension during hospitalization for a leg fracture and was started on one antihypertensive medication.
- **2 years ago**, his BP became poorly controlled, and he was noted to have worsening kidney function.
- **1 year ago**, his BP became uncontrolled again, and medications were increased.
- He denied hematuria, foamy urine, or changes in urine output at that time; however, he had a history of recurrent right flank pain.

- **Physical exam.:** BP 160/90 mmHg (all ext.), liver span 13 cm., no abdominal bruit, no edema

Further Hx & PE ?
How to approach ?

Case 3

- **A 40-year-old man presented with hypertension** “ตรวจพบความดันโลหิตสูง”

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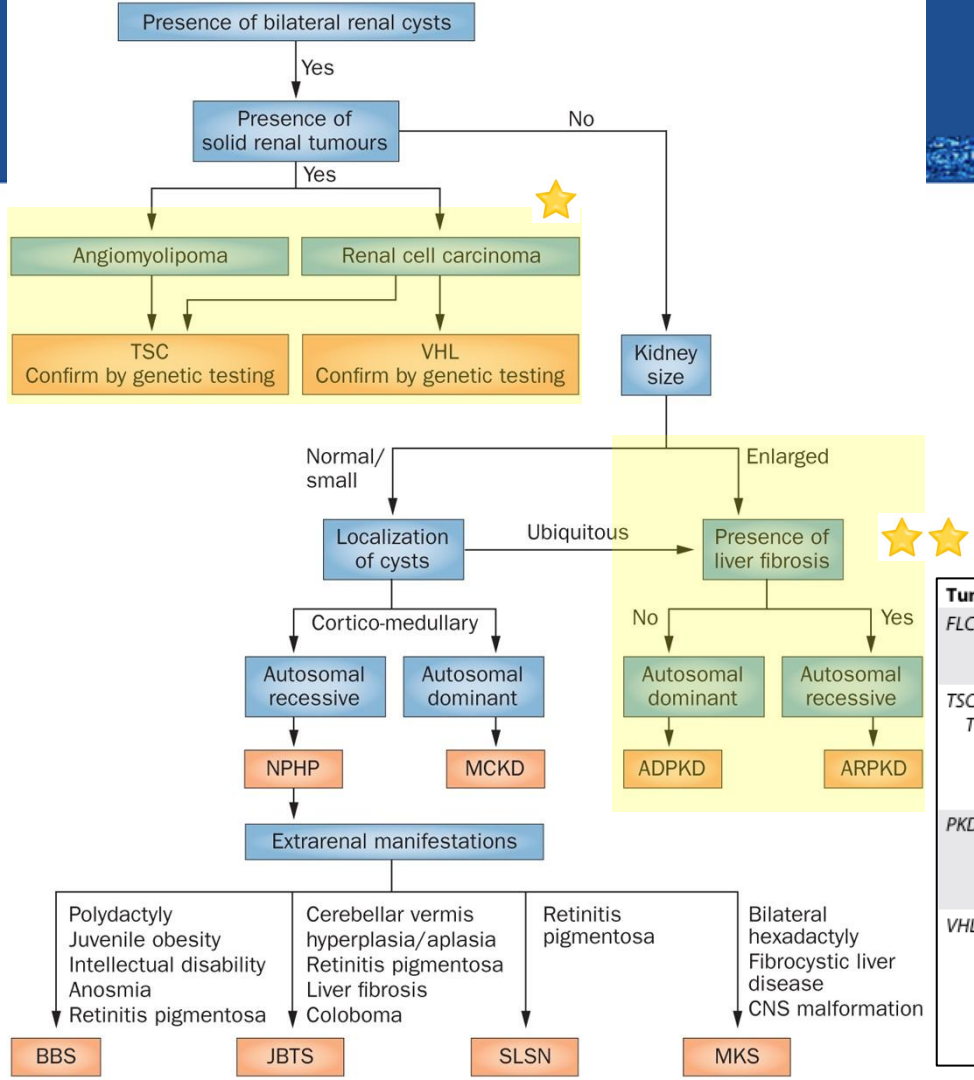
- He denied hematuria, foamy urine, or changes in urine output at that time; however, he had a history of recurrent right flank pain.

- **Physical exam.:** BP 160/90 mmHg (all ext.), liver span 13 cm., no abdominal bruit, no edema, bimanual palpation positive both sides

Further Hx & PE ?
How to approach ?

Polycystic kidney disease



Cystic kidney disease

- **Size of kidney**
- Extra-renal manifestation/tumor
- Familial history

Tumorous disorders				
FLCN	Birt-Hogg-Dubé syndrome	AD	Kidney cysts	Hair follicle hamartomas, kidney tumors, spontaneous pneumothorax, lung cysts
TSC1 *TSC2*	Tuberous sclerosis complex (TSC)	AD	Kidney cysts	Multisystem disorder with hamartomas in brain, skin, heart, kidneys (angiomyolipomas), and/or lung, plus CNS manifestations: epilepsy, learning difficulties, behavioral problems
PKD1/TSC2	*PKD1/TSC2*-Contiguous gene syndrome (CGS)	AD	Severe, infantile PKD	Hamartoma and CNS manifestations of TSC
VHL	Von-Hippel-Lindau syndrome	AD	Kidney and pancreatic cysts	Familial cancer syndrome with malignant and benign neoplasms in retina, cerebellum, spinal hemangioblastoma, RCC, pheochromocytoma, and pancreatic tumors

Polycystic kidney disease

ADPKD

- A group of inherited disorders
- Kidney cyst + extra-renal manifestation
- Single pathogenic variants
- AD inheritance (De novo 20%)

ADPKD - (causal gene)

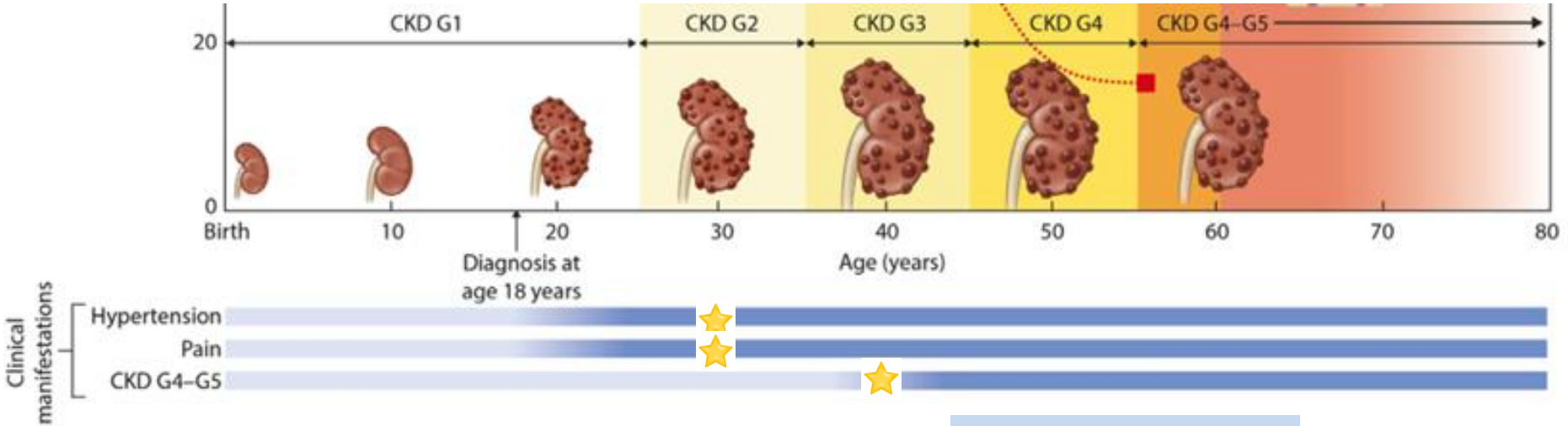
PKD 1	PKD 2
Chromosome 16	Chromosome 4
Codes Polycystin 1 protein (PC1)	Codes Polycystin 2 protein (PC2)
More severe phenotype	Less severe phenotype
ESKD 4-5th decade	ESKD 6-7th decade
Incidence: 85%	Incidence: 15%

AJKD 2025

Gene	Screened Families	No. of Families[a]	Disease Designation	Kidney Phenotype	Extrarenal Phenotype	Comments
Major ADPKD Genes and Nomenclature for Unknown, Not Screened, and Unresolved Typical Cases						
Unknown, or not screened, or unresolved			ADPKD	Bilateral PKD; kidney enlargement; age-related CKD, may result in KF	Liver cysts including severe PLD; increased risk of ICA	Wide phenotypic range in terms of TKV and KF risk and timing
PKD1	~48%	>3,250	Truncating pathogenic variant: ADPKD-*PKD1*	Bilateral PKD; early kidney enlargement; CKD G3, age ~40 y; KF in 50s	Liver cysts including severe PLD; increased risk of ICA	Some disease variability, including a more benign course, sometimes associated with mosaicism
	~19%	>1,750	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%	>1,000	ADPKD-*PKD2*	Bilateral PKD; milder and later kidney enlargement; CKD G3, age ~55 y; KF in 70s	Liver cysts including severe PLD; increased risk of ICA	Some disease variability, including a more severe or more benign course
Minor ADPKD Genes With Definitive-to-Moderate Evidence of Disease Involvement[b]						
ALG5	<0.5%	<10	ADPKD-*ALG5*	Mild to moderate cyst development with limited kidney enlargement and fibrosis; CKD and some KF in older adults[1]	A few liver cysts in a minority of people	
ALG9	<0.5%	<20	ADPKD-*ALG9*	Mild to moderate cystic disease with significant CKD in older adults[2]	Liver cysts common	Biallelically, associated with the congenital disorder of glycosylation, type IL (CDG1L)
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[3,4]	Liver cysts, usually mild; ICA and vascular risk possible	ADPKD-*DNAJB11* has similarities to ADTKD, because of the small, fibrotic kidneys, but visible cysts are usually present. Biallelically, associated with renal-hepatic- pancreatic dysplasia[5]
GANAB	<0.5%	<20	ADPKD-*GANAB*	Mild cyst development; limited CKD, no KF[6]	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[7]	Liver cysts only rarely seen, with risk of ICA unclear	Biallelically, associated with short-rib thoracic dysplasia (*SRTD9*) and retinitis pigmentosa (*RP80*)
NEK8	<0.5%	<20	ADPKD-*NEK8*	Bilateral PKD, kidney enlargement; KF in childhood, occasionally later in cases of specific alleles or mosaicism[8]	Liver cysts rare	De novo occurrence was reported in 75% of reported cases. Biallelically, associated with renal-hepatic-pancreatic dysplasia and nephronophthisis (*NPHP9*)
Suspected Monoallelic PKD Genes With Limited Evidence of Disease Involvement or Not Assessed[b]						
ALG6	<0.5%	<10	ADPKD (only when phenotype consistent with this diagnosis)	Generally mild with or without persevered kidney function[9]	Liver cysts, including severe PLD	Can present with mainly a liver phenotype. Monoallelic *ALG6* is likely a lower-penetrant phenotype. Biallelically, associated with the congenital disorder of glycosylation, type IC (CDG1C)

ADPKD

Clinical manifestation



ESKD PKD1 56-68 y
PKD2 78 y

Kidney enlargement 30-40 y

Liver enlargement >30 y

KDIGO 2025

ADPKD

Clinical manifestation

Manifestation	Prevalence	Comments
Renal		
Urinary concentration defect[a]	Up to 60% of children	Earliest manifestation of mild polyuria is often undetected
Hypertension[a]	• 50–70% of patients prior to GFR decline • Average age of onset is 30 years • At least 20–40% of children	Screen children with family history of ADPKD from 5 years of age, then at 3-year intervals if negative for hypertension
ESRD[a]	50% of patients by 60 years of age	Mean age of onset of 56 years (truncating *PKD1* mutations), 68 years (non-truncating *PKD1* mutations) or 78 years (*PKD2* mutations)
Proteinuria (>300 mg/day)	Associated with GFR decline	Prognostic marker of ADPKD
Abdominal or flank pain	>60% of adult patients	• Acute or chronic • Multiple causes
Nephrolithiasis	20–35% of adult patients	Uric acid and/or calcium oxalate stones
Cyst haemorrhage and/or gross haematuria	Up to 60% of adult patients	Most haemorrhages resolve within 2–7 days without intervention
Urinary tract infection[a]	30–50% of adult patients	More common in women than in men
Renal cell carcinoma	<1% of adult patients	Risk not increased compared with the general population, but patients can present with systemic symptoms of cancer

Nature review 2018

ADPKD

Clinical manifestation

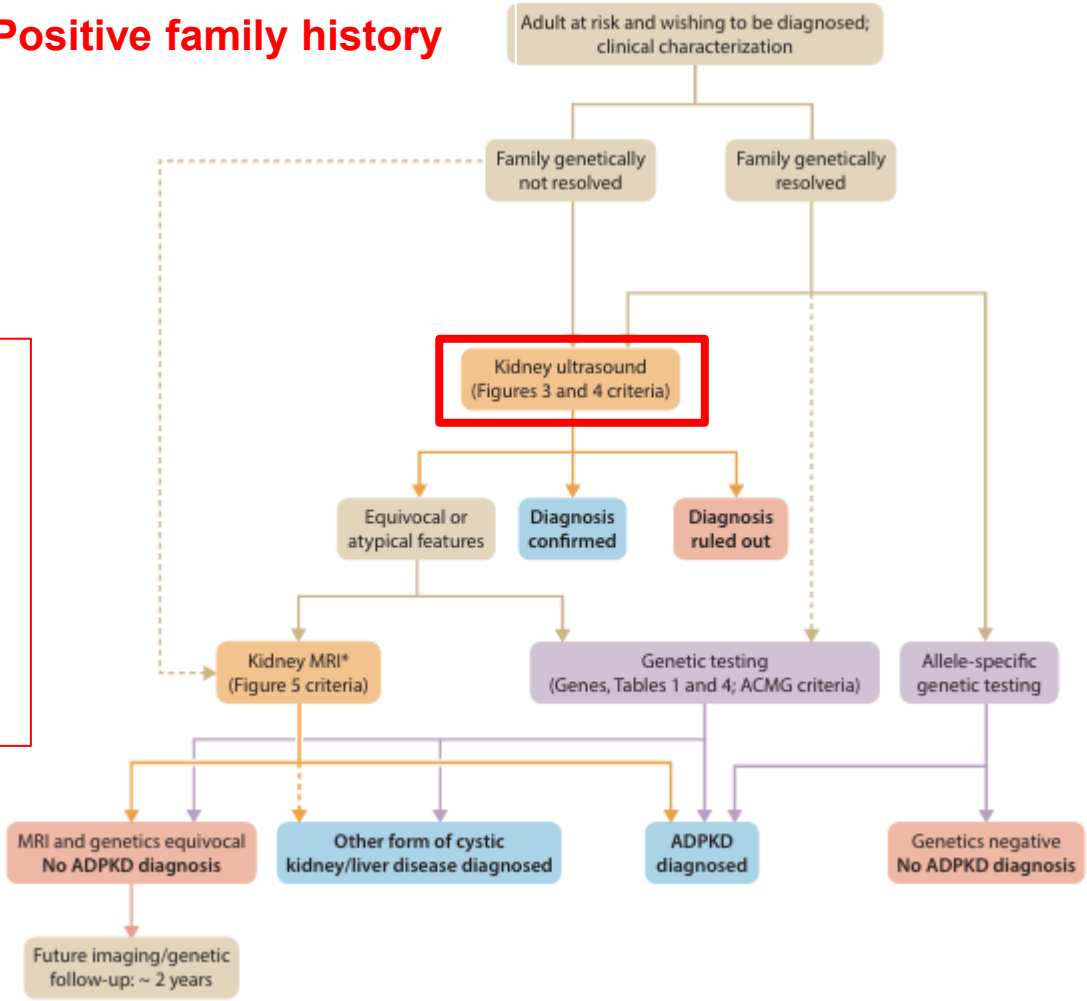
Extrarenal		
Polycystic liver disease	>80% of patients by 30 years of age	Include liver imaging in initial visit; further follow-up dependent on result of imaging
ICA	• 8% of all adult patients • 21% of adult patients with a family history of ICA	Screen if family history of subarachnoid haemorrhage or ICA, personal history of intracranial haemorrhage, individuals working in high-risk professions and before major elective surgery (including before transplantation)
Arachnoid cysts	8% of adult patients	Possible increased risk of spontaneous subdural haematoma
Mitral valve prolapse or bicuspid aortic valve	Up to 25% of adult patients	Screen when there is a heart murmur or symptoms
Idiopathic dilated cardiomyopathy or left ventricular non-compaction	Rare	Screen when there is a family history of these conditions
Pericardial effusion	Up to 35% of adult patients	Screen if symptoms of pericardial effusion are present
Pancreatic cysts	10% of adult patients	No screening needed
Diverticulosis	Up to 50% of patients with ESRD	Increased risk of diverticulum perforation following renal transplantation
Bronchiectasis	Up to 35–40% of adult patients	Mild; no screening needed
Congenital hepatic fibrosis[a]	Rare (on the basis of case reports)	No screening needed
Seminal vesicle cysts	Up to 40% of men	No correlation to semen abnormalities
Male infertility	Associated with ADPKD	Abnormal semen parameters reported

Nature review 2018

Diagnosis ADPKD

- DDx of kidney cysts
- Positive or Negative ⭐ family history
- Kidney cyst count ⭐
  - > Age
  - > Dx or R/O

Positive family history



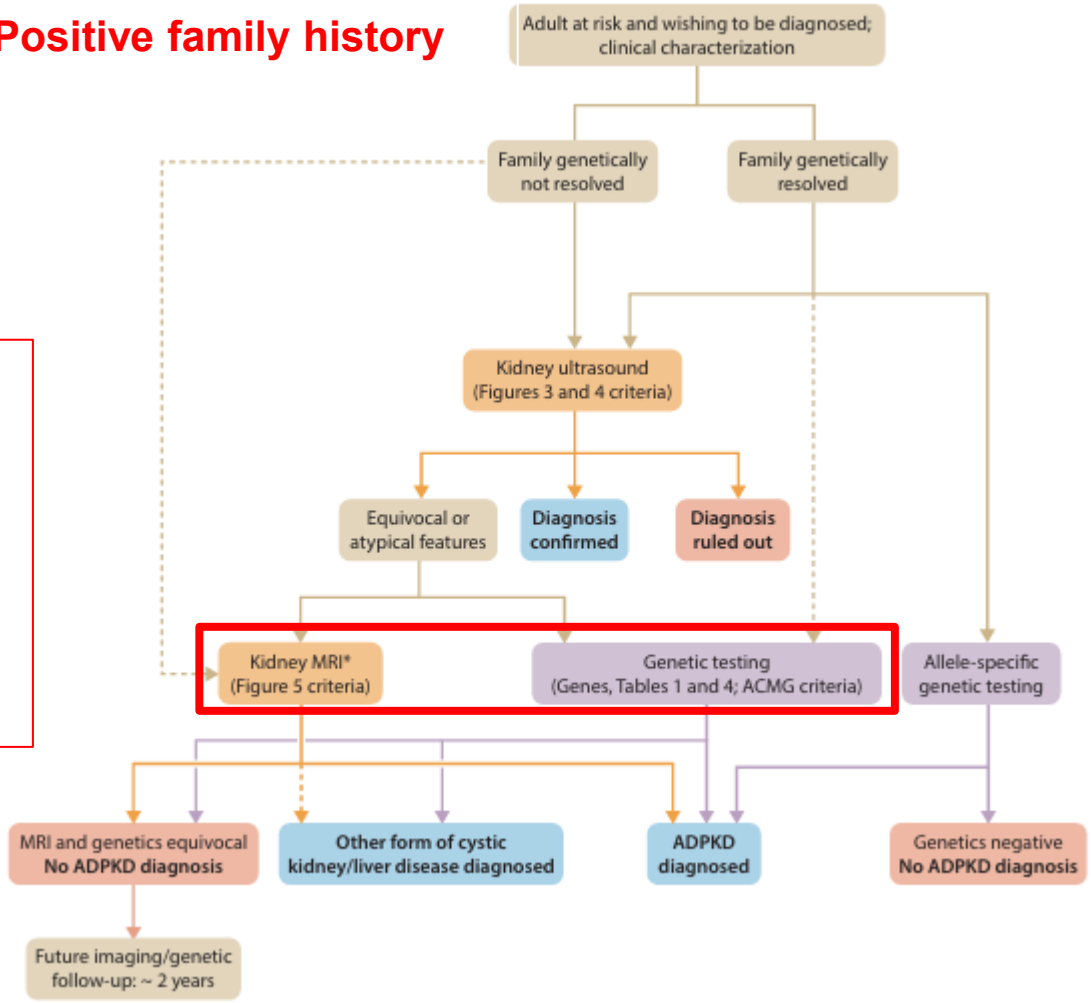
KDIGO 2025

Ultrasound criteria by age group to ***diagnose*** ADPKD when there is a positive family history ⭐							
Age (years)	Number of cysts (test criterion based on number of cysts)	ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown gene type	
		Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive test (%)	Sn (%)	Predictive value based on a positive 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 by age group to ***exclude*** ADPKD when there is a positive family history							
Age (years)	Number of cysts (test criterion based on number of cysts)	ADPKD-*PKD1*		ADPKD-*PKD2*		Unknown gene type	
		Predictive value based on a negative test (%)	Sp (%)	Predictive value based on a negative test (%)	Sp (%)	Predictive value based on 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

Diagnosis ADPKD

- DDx of kidney cysts
- Positive or Negative family history
- Kidney cyst count
  - > Age
  - > Dx or R/O



KDIGO 2025

Diagnosis ADPKD

Magnetic resonance imaging (MRI) criteria for ages 16-40 years in people with a positive family history					
Age (years)	**Number of cysts (test criterion based on number of cysts)**	**Predictive value based on a positive test (%)**	**Sensitivity (%)**	**Predictive value based on a negative test (%)**	**Specificity (%)**
16–29	≥10 cysts	100	100		
30–40		100	100		
16–29	≥5 cysts			100	98.3
30–40				100	100

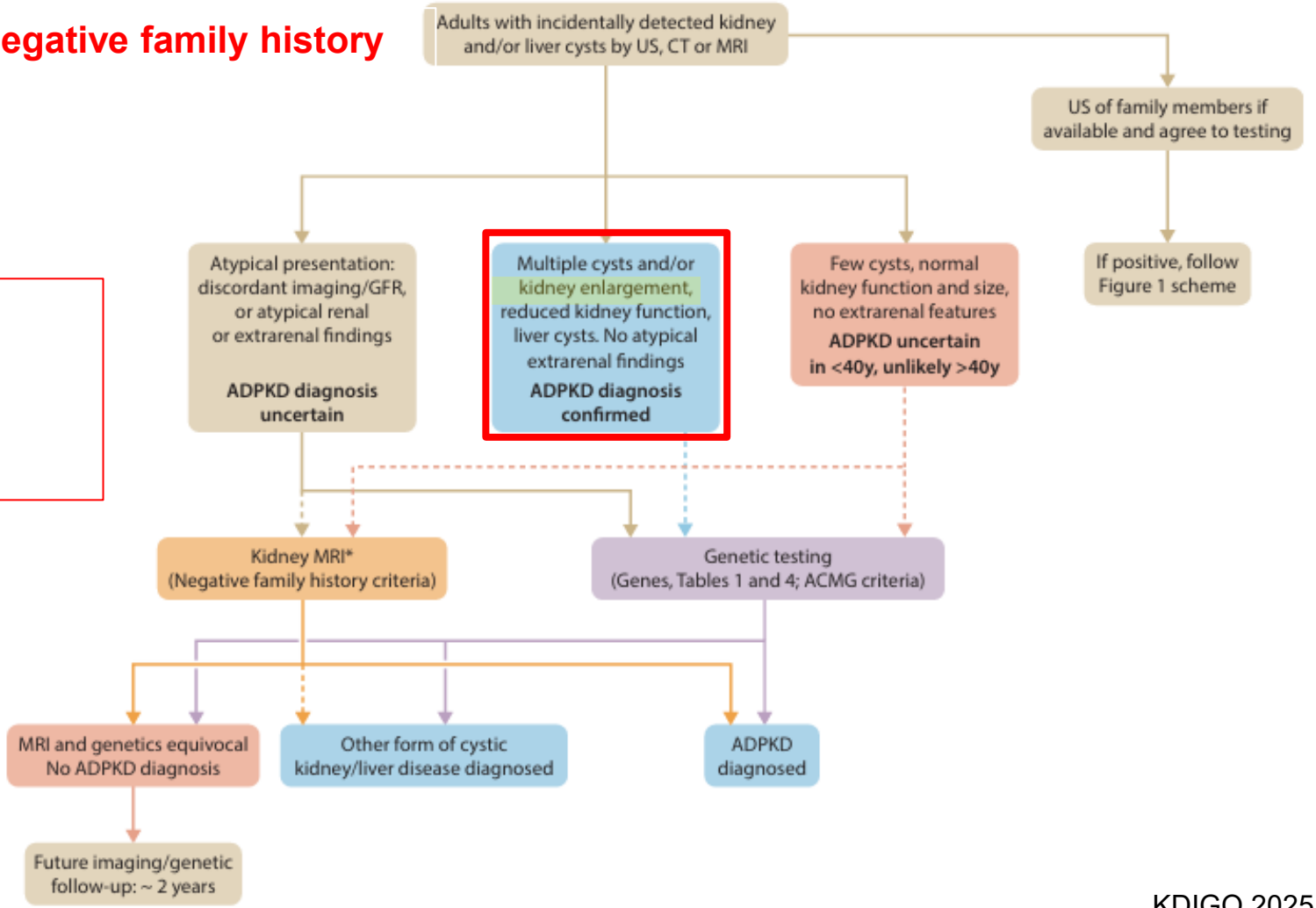
Figure 5 | Magnetic resonance imaging (MRI) criteria for ages 16–40 years in people with a positive family history.[31] The sensitivity of a test is its ability to designate an individual with the disease as positive. The specificity of a test is its ability to designate an individual who does not have the disease as negative.

Diagnosis

ADPKD

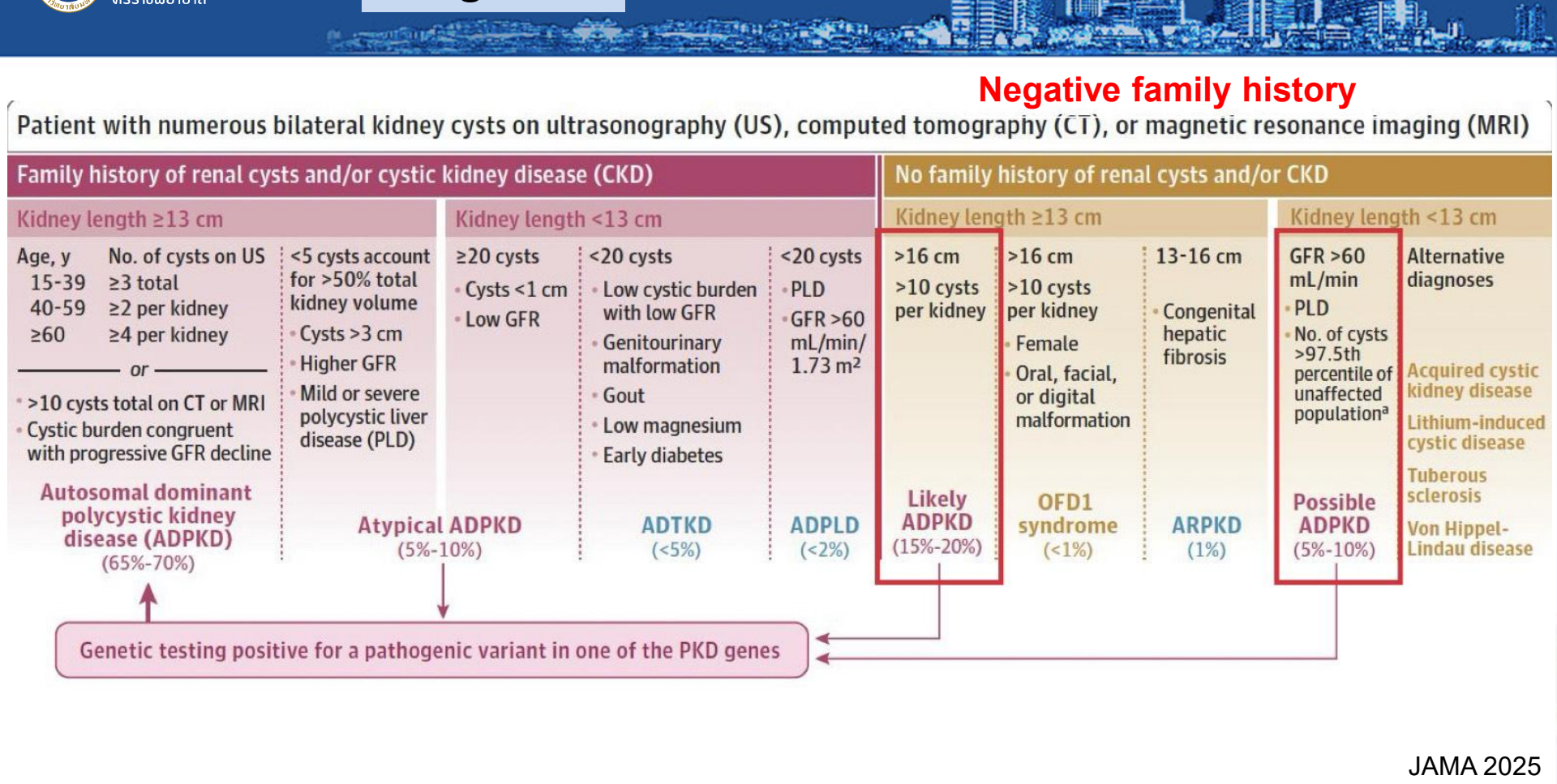
- DDx of kidney cysts
- Positive or Negative family history
- Kidney cyst count
  - > Age
  - > Dx or R/O

Negative family history



KDIGO 2025

Diagnosis ADPKD



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Diagnosis ADPKD

Table 4 | Situations in which genetic testing can clarify the diagnosis and aid in determining a 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 findings with imaging, such as asymmetric or unilateral disease	Positive result can show a genetic origin (including mosaicism or minor gene involvement).
Discordance between structural (MIC) and functional (GFR) ADPKD severity[a]	Genetic testing may reveal an atypical form of the disease or additional genetic or contributory factors, but nongenetic factors may also be important.
Negative family history	Positive result can show a genetic origin (*de novo* mutation can be proven).
Very-early-onset (VEO) ADPKD	Biallelic disease may be found (Chapter 9).
Related living transplant donor (aged <30 yr, especially if a few cysts detected)	Genetic testing can exclude the familial variant, if known, and test for other genetic causes.
Family planning and preimplantation genetic diagnosis (PGD)	Obtaining a genetic diagnosis can aid in family planning and enable PGD (Chapter 8).
All people	Genetic testing can confirm the diagnosis, identify the responsible gene and variant, and provide prognostic information.

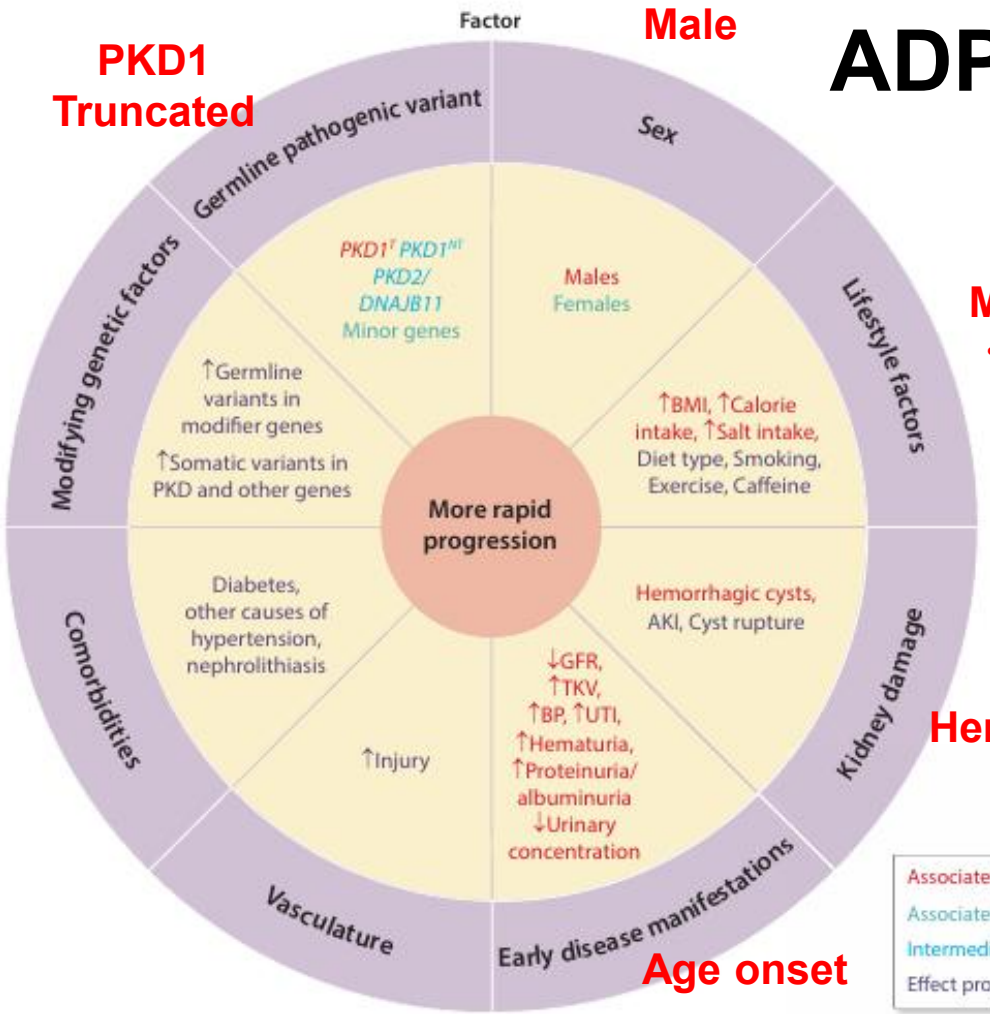
ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; MIC, Mayo Imaging Classification (see definition in Chapter 9); PGD, preimplantation genetic diagnosis.

[a]Discordance may be reduced GFR without significant kidney enlargement, or an older adult with large kidneys but normal GFR.

For more information about mosaicism, and biallelic and digenic inheritance, see Practice Point 1.3.12.

Management

Prognosis assessment ⭐



PKD1 Truncated

Male

ADPKD

Metabolic ทำตัวเอง

Hemorrhagic cyst

Age onset

Management

Prognosis assessment ★

PROPKD: 7-9
MIC: E, D

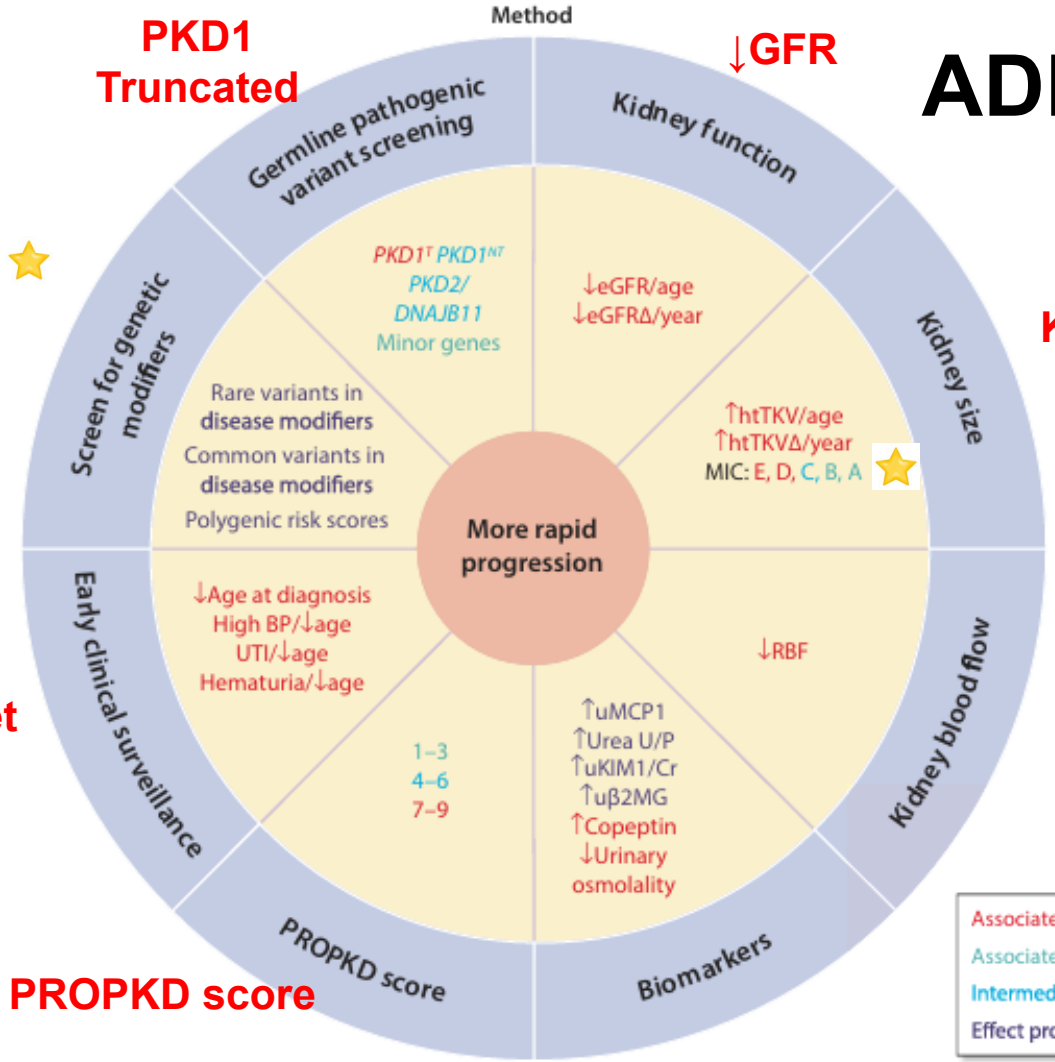
Age onset

PKD1 Truncated

↓GFR

ADPKD

Kidney size/y or /age

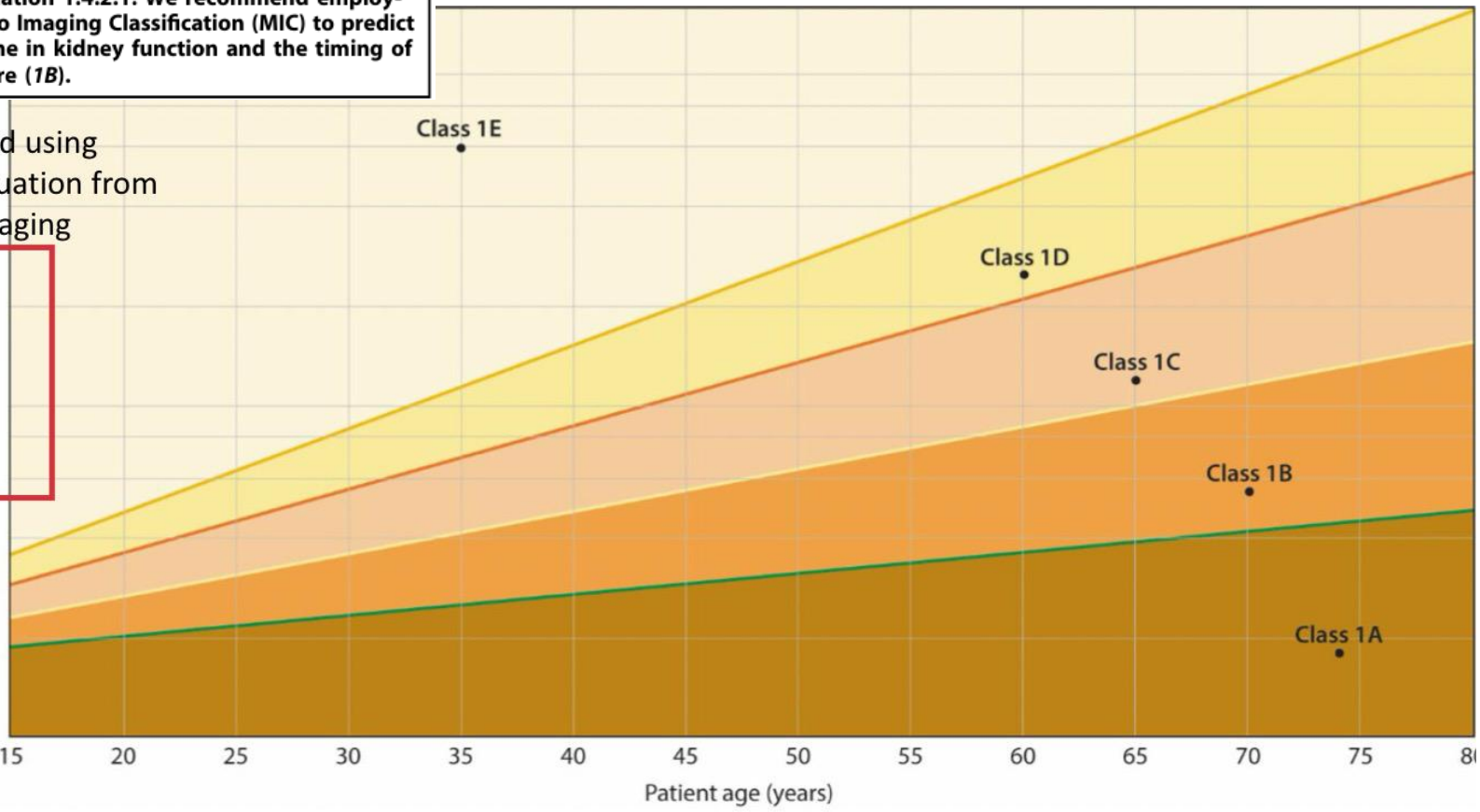


★ **PROPKD score**

Mayo Imaging Classification (MIC)

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

Calculated using ellipsoidal equation from MRI imaging



PROPKD score

Variable	Points
being male	1
hypertension before 35 years of age	2
first urologic event* before 35 years of age	2
mutation	
PKD2 mutation	0
nontruncating *PKD1* mutation	2
§truncating *PKD1* mutation	4
PROPKD Score =	**SUM**

Sample PROPKD Score Calculation

ADPKD patient info: 29 year old male with hypertension and a truncating *PKD1* mutation

1 point for being male
2 points for hypertension before 35 years of age
+**4** points for a truncating *PKD1* mutation

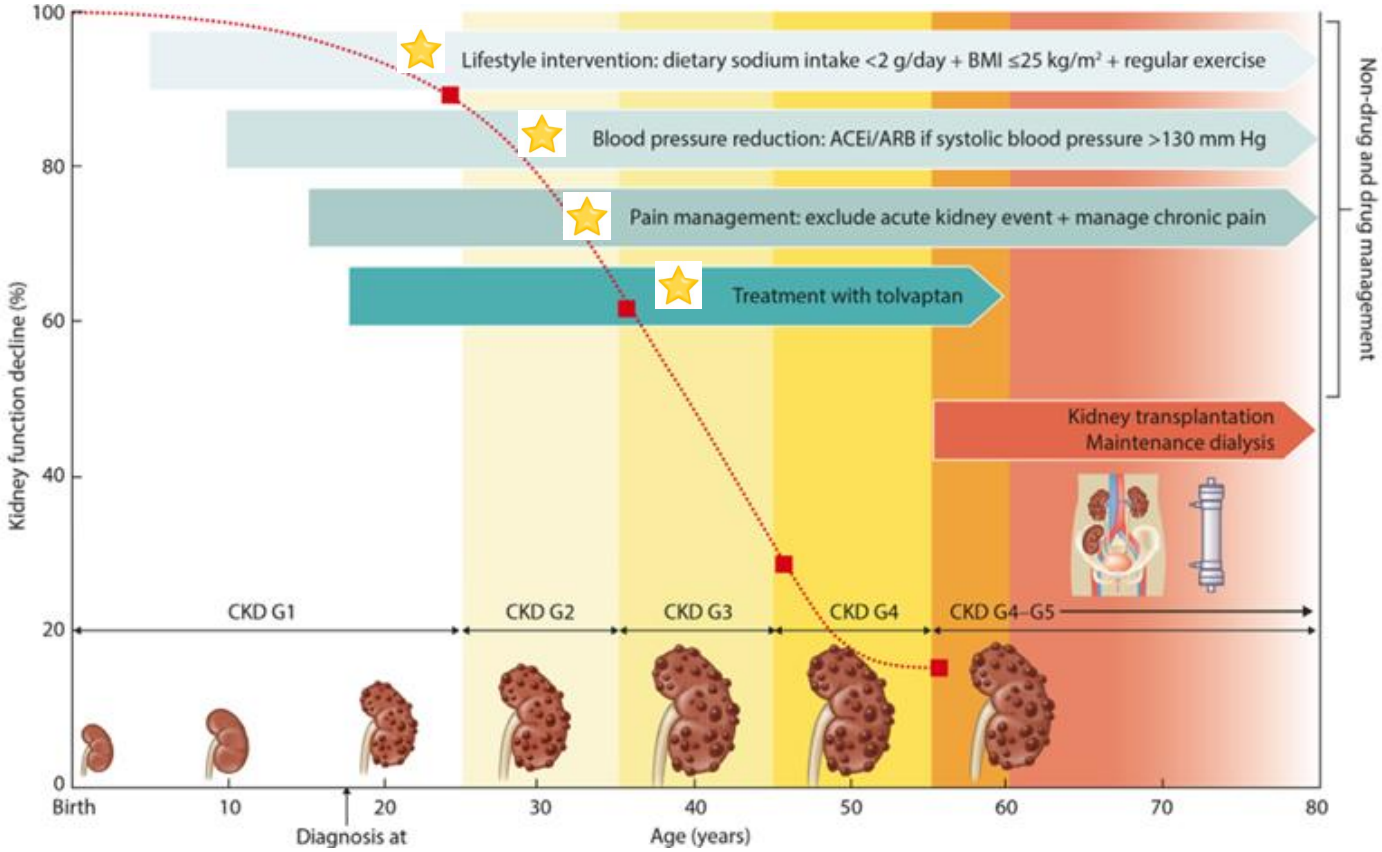
7 points **PROPKD Score**

HIGH Risk of Progression to ESKD

Total Points

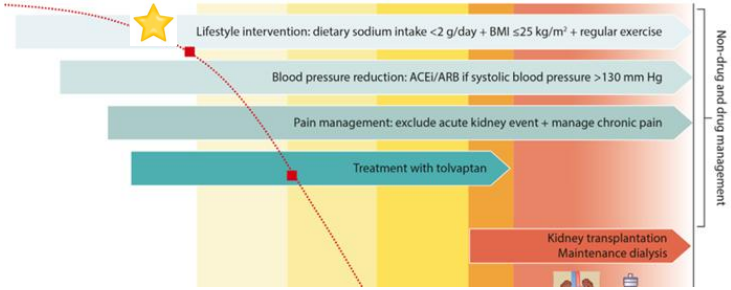
PROPKD Score	0	1	2	3	4	5	6	7	8	9
Risk of Progression to ESRD	**LOW** **70.6 median age for ESRD onset** Eliminates evolution to ESRD before age 60† †negative predictive value of 81.4%				**INTERMEDIATE** **56.9 median age for ESRD onset**			**HIGH** **49 median age for ESRD onset** Risk of rapid progression and a 92% chance of reaching kidney failure before age 60.		

ADPKD Management



ADPKD

Management



Lifestyle

- Water ≥2 l/day
- Sodium <2 g/day, salt <5 g/day
- Protein 0.8–1 g/kg/day
- Calories 25–35 kcal/kg/day
- Fat <30% of daily energy intake
- Fiber 25–38 g/day
- Caffeine <400 mg/day

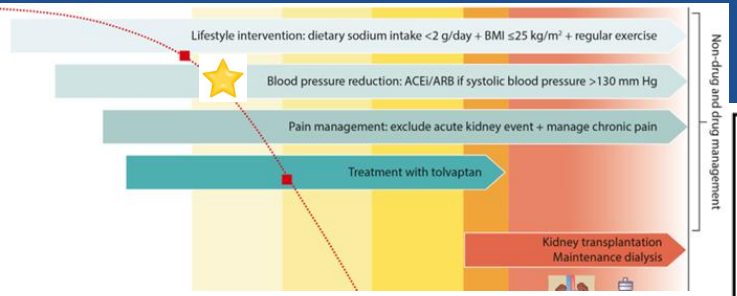
- Avoid tobacco products
- Limit alcohol intake:
  ≤2 drinks/d (M), ≤1 drink/d (F)
- Counsel patients about the use of cannabis products
- Avoid recreational drugs and nephrotoxins

- Maintain BMI 20–25 kg/m²
- Avoid sarcopenia

- Exercise >150 min/week
- Strength training >2/week
- Avoid collision exercise

ADPKD

Management



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 of ≤110/75 mm Hg as measured by HBPM, if tolerated (*1D*).

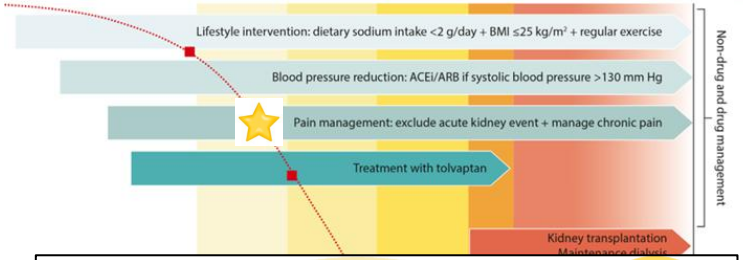
Recommendation 2.1.4: For people with ADPKD aged ≥50 years with any stage of CKD (CKD G1-G5), we suggest a target mean systolic blood pressure (SBP) of <120 mm Hg, if tolerated, as assessed using standardized office BP measurement (*2C*).

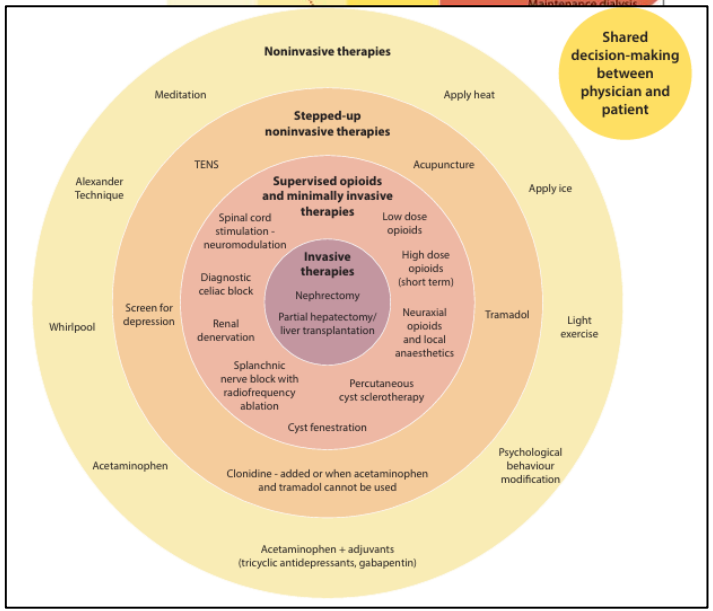
BP control

Hypertension in ADPKD		
Monitoring	**Non-pharmacologic interventions**	**Medical management**
• Standardized office BP measurement in preference to routine office BP measurement • HBPM is preferred to office only measurements • Consider ABPM in children and adults with difficult BP control, LVH, proteinuria, or declining kidney function but normal office BP readings • 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 • Optimize body weight with a healthy diet and regular exercise • Optimize pain management	• Inhibition of RAS provides the cornerstone of BP management and includes the use of an ACEi or ARB • Optimize BP with a 2nd-line agent, if needed • Individualized therapy is indicated

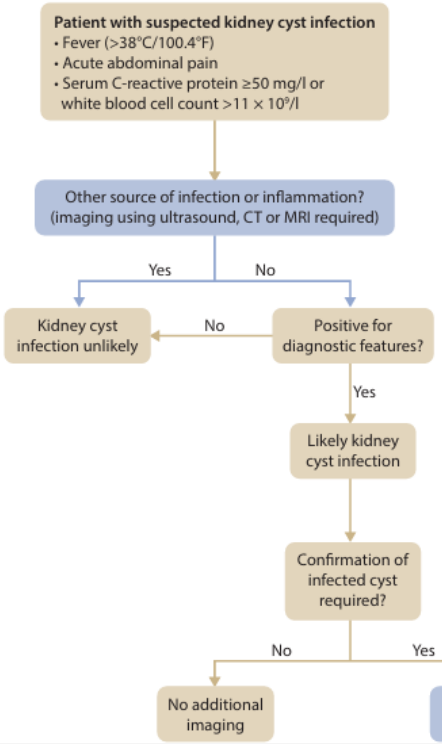
Figure 14 | Blood pressure (BP) management in autosomal dominant polycystic kidney disease (ADPKD). ABPM, ambulatory BP-monitoring; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HBPM, home BP-monitoring; LVH, left ventricular hypertrophy; RAS, renin–angiotensin system.

ADPKD Management





Complications: hematuria/pain/infection/stone



Diagnostic features
Diagnostic features considered positive in the presence of at least two items from at least 2 categories:

Clinical factors
1. Acute pain or tenderness in kidney area
2. Symptoms of urinary tract infection
3. Recent instrumentation of urinary tract
4. Immune compromised patient (including patients on dialysis)

Microbiology
5. Positive urine and/or blood culture
6. Positive cyst fluid culture

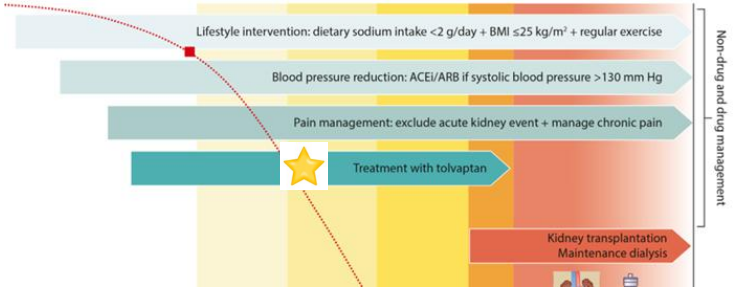
Imaging
7. Imaging (ultrasound, CT, or MRI) before and after onset of symptoms demonstrating a new complex cyst
8. Intracystic gas (ultrasound, CT, or MRI)
9. Pericystic inflammation (CT or MRI)
10. Fluid-fluid levels in a cyst (MRI)
11. Thickened cyst wall (CT or MRI)
12. Contrast enhancement in the 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 Ga-67 abnormal uptake by a cyst
15. ^{111}Indium-white blood cell scan showing accumulation in a cyst

Treatment
16. Clinical response to antibiotic treatment

Table 8 | Approaches to reduce AVP activity in ADPKD

Factors	Increased water intake	V_2 receptor antagonist (tolvaptan)
Mechanism	Suppression of AVP release by lowering plasma osmolality	Selective blockade of AVP binding on V_2 receptors
Administration	Drinking water during waking hours	Split-dose tablet (1 tablet upon waking, and 1 tablet 8 h later)
Effect on water intake	Voluntary increase (≥2 l/d)	Involuntary increase due to thirst and aquaresis (>3–7 l/d)
Effect on circulating level of AVP	Reduced level	Increased level
Indication for use in ADPKD	All people with eGFR >30 ml/min per 1.73 m^2	Selected high-risk groups due to cost and side effects
Efficacy to ↓ urine osmolality to 300 mOsmol/kg	~50% of participants in 3-yr (PREVENT-ADPKD trial)[257]	~70% of ADPKD participants, >3 yr treatment in the TEMPO 3:4 trial
Efficacy to ↓ TKV in ADPKD	No (PREVENT-ADPKD trial)[257]	Yes (TEMPO 3:4)
Efficacy to ↓ long-term eGFR decline	No	Yes (~1 ml/min per 1.73 m^2) (TEMPO 3:4 and REPRISE trials)[28,29]
	No data on risk reduction for CKD G5 (PREVENT-ADPKD trial)[257]	No data on risk reduction for CKD G5
Adherence to treatment	~50% over 3 yr (PREVENT-ADPKD trial)[257]	Real-world adherence declines over time and ~75% after 3 yr[377,378]
Disadvantages	Long-term adherence is poor; pollakiuria, polyuria	Thirst/dehydration
	Reversible mild hyponatremia	Pollakiuria, nocturia, polyuria with potential impact on day-to-day living (occupation, habits)
	Environmental issues (bottled water)	Blood tests (every 1–3 mo)
		Hypernatremia; hyperuricemia
		Risk of hepatotoxicity
		Accessibility
Advantages	Access and low cost (tap water)	Standard dose
	More physiological suppression of AVP than V_2 receptor antagonist	Better 24-h inhibition

ADPKD Management



Tolvaptan

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

***Rapid progression**

***Mayo 1C**

***Hx eGFR decline**

Initiation of tolvaptan should be offered to adults with ADPKD and:
eGFR ≥25 ml/min per 1.73 m²

AND

Risk of rapid disease progression* as indicated by either:
Mayo class 1C† to 1E
OR
Historical rate of eGFR decline‡ (≥3 ml/min per 1.73 m² per year)

Figure 25 | The Kidney Disease: Improving Global Outcomes algorithm to decide in whom to prescribe tolvaptan. *Rapid disease progression is defined as having reached or being expected to reach kidney failure due to autosomal dominant polycystic kidney disease (ADPKD) before age ~60 years, the average age at which untreated people with ADPKD reach kidney failure. The use of age ~60 years is based on multiple cohort studies (not stratified by genotype) (European Renal Association–European Dialysis and Transplant Association [ERA-EDTA], mean age 58 years[379]; Genkyst cohort, 61.7 years[36]; Mayo PKD Database, 62 years[380]; Korea national cohort, 62 years[379]; and Australia and New Zealand Dialysis and Transplant Registry (ANZDATA registry), 60 years.[381] †Because some people with MIC subclass 1C may not have rapid disease progression, clinical judgment and evaluation should be made on a case-by-case basis and additional information could be used, particularly in the people with age-adjusted height-adjusted total kidney volume (htTKV) on the borderline of Mayo Image Classification 1B, to assess the risk for rapid disease progression (e.g., evidence of estimated glomerular filtration rate [eGFR] decline or of a reduced age-calibrated eGFR.[382] Predicting Renal Outcome in Polycystic Kidney Disease [PROPKD] score >6, family history with onset of kidney replacement therapy [KRT] at <60 years in ≥2 first-line family members, or novel biomarkers).[205] ‡If estimated glomerular filtration rate (eGFR) loss has likely alternative explanations (e.g., vascular disease, uncontrolled hypertension, diabetic nephropathy, proteinuria ≥1 g/d) and/or acute kidney injury, then initiation of tolvaptan use should be re-evaluated, even in the presence of rapid eGFR decline. In these cases, additional information (including magnetic resonance imaging or computed tomography imaging should be undertaken, if not previously performed; PROPKD score >6, a family history with onset of KRT at age <60 years in ≥2 first-line family members) should be acquired to ensure ADPKD as the primary reason for eGFR loss.

Extra-renal manifestation

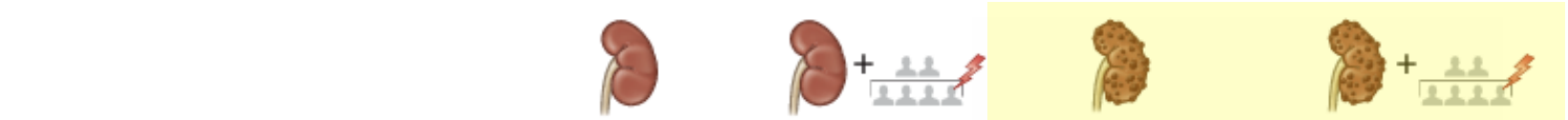
Extrarenal manifestations described in ADPKD	Estimation of the % of people affected by ADPKD	Details or notes	Guidance for imaging
Central nervous system manifestations			
Intracranial aneurysm	Summary: 12.9% (95% CI: 10.4%–15.4%)	Prevalence in ADPKD population is difficult to assess because systematic screening is usually not performed.	See Recommendation 6.1.2 and Practice Point 6.1.6.
Subarachnoid hemorrhage	Summary: Incidence rate 0.57 per 1000 patients/yr (95% CI: 0.19–1.14)	Thunderclap headache should lead to immediate medical attention.	Only if symptoms are present
Thoracic aortic aneurysm	~1.5%[620,631]	See Practice Point 6.2.2.	No systematic screening. To be considered in case of positive familial history
Thoracic aortic dissection	Very rare case reports[632,637,640]	Acute chest/upper back/abdominal pain is present in >90% of the cases.	Only if symptoms are present
Coronary artery dissection	Very rare case reports[629]	People generally present with symptoms and signs characteristic of acute myocardial infarction. Usually more frequent in young women	Only if symptoms are present
Carotid and vertebral artery dissection	Very rare case reports[625]	Often result in ischemic stroke or transient ischemic attack, often associated with neck pain or headaches Occasional Horner syndrome in case of carotid	Only if symptoms are present
Hepatic and gastrointestinal manifestations			
Symptomatic polycystic liver disease	<5% predominant in females	Liver cysts are present in >80% by age 30 yr.	Include liver imaging in initial visit (Chapter 5)

ADPKD Management

Extra-renal manifestation

6.1 Intracranial aneurysms ⭐

Recommendation 6.1.1: We recommend informing adults with ADPKD about the increased risk for intracranial aneurysms (ICAs) and subarachnoid hemorrhage (SAH; Figure 35) (*1C*).



	General population	General population with family history of ICA or SAH	ADPKD population	ADPKD population with family history of ICA or SAH
Prevalence of ICA (95% CI)	2.9% (1.9–4.5)	3.4 (1.9–5.9) higher risk[a]	12.9% (10.4–15.4) (Figure 36)	17.1% (13.4–21.1)[b]
Incidence rates of SAH (per 1000 person-years, 95% CI)	0.079 (0.069–0.09)[c]	3–7 higher risk	0.57 (0.19–1.14) (Figure 37)	Likely higher (based on data from general population)

Figure 35 | Prevalence of unruptured intracranial aneurysms (ICAs) and incidence of subarachnoid hemorrhage (SAH) in the general and autosomal dominant polycystic kidney disease (ADPKD) populations, overall and in the presence of a family history of ICA or SAH.

ADPKD Management

Recommendation 6.1.2: We recommend screening for ICA in people with ADPKD and a personal history of SAH or a positive family history of ICA, SAH, or unexplained sudden death in those eligible for treatment and who have a reasonable life expectancy (*1D*).

Table 15 | Risk factors for ICAs or SAH

Evidence	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 when first-degree relative)—*Strong* • Personal history of SAH or ICA—*Strong* • Tobacco smoking (especially >20 pack-years)—*Strong* • Female sex—*Moderate* • *PKD1* genotype—*Moderate* • Uncontrolled hypertension—*Moderate* • Early-onset hypertension (age <35 yr)—*Moderate* • Severity of ADPKD—*Weak*
Evidence in non-ADPKD population	• Japanese or Finnish ancestry • Alcohol in large quantity (risk factor for ICA rupture)

Secondary hypertension: Approach

1. **Clues to secondary HT**
   - 1.1) Character of HT
   - 1.2) Clinical setting / syndrome
2. **DDx: Clinical**
   - **2.1) Endocrine HT**
     - ➔ DDx แม้ไม่มี Clues: PA, Pheo.
     - ➔ มีClinical clues: Cushing, Thyroid, Acromegaly, Pheo.
     - ➔ Genetic endocrine “esp. Pheochromocytoma”
   - **2.2) HT + Hypokalemia (**ถ้าซักประวัติได้**)** ➔ PAC / PRA
   - **2.3) Kidney disease** ➔ RVD / PKD / Glom.
   - **2.4)** อื่น ๆ เช่น **CVS /** ยา / Monogenic HT: AME / Gordon / Liddle
3. **Review of systems/PE, target organ damage, co-morbidity, drugs**
4. **Investigation**