Brigham and Women's Hospital
Founding Member, Mass General Brigham

# Adrenal Disorders

**Anand Vaidya, MD MMSc**
Director, Center for Adrenal Disorders
Chief (Interim), Division of Endocrinology, Diabetes, & Hypertension
Brigham and Women's Hospital
Associate Professor of Medicine, Harvard Medical School
anandvaidya@bwh.harvard.edu

# Disclosures

**No financial disclosures related to the contents of this presentation**

**Unrelated financial disclosures:**

Consulting: HRA Pharma, Mineralys, Corcept

Research Funding: National Institutes of Health, Doris Duke Charitable Foundation, Ventus Charitable Foundation

**Training**

- Harvard Medical School
- Internal Medicine Residency @BWH
- Clinical Endocrinology Fellowship @BWH
- Cardiovascular Endocrinology Research Post-Doc @BWH

**Positions**

- Director, Center for Adrenal Disorders @BWH
- Chief (Interim), Division of Endocrinology, Diabetes, and Hypertension @BWH
- Associate Professor of Medicine @HMS
- Director, e-Learning Initiative @BWH/@NEJM
- Former Director, Homeostasis II Curriculum @HMS

# Learning Objectives

1. To provide a updates and pragmatic approaches to **primary aldosteronism and hypertension**

2. To provide a pragmatic approach to evaluation of **adrenal insufficiency**

3. To provide a pragmatic approach to the assessment of incidentally discovered **adrenal masses**

# Primary Aldosteronism

# Case

36-year old woman presents for hypertension management

Age 27: 1st pregnancy, preeclampsia => Persistent HTN => nifedipine

| Age 28 (CCB) | Age 32 (no meds) | Age 33 (CCB, **ACEi**) | Age 36 (CCB, **ACEi**) |
|---|---|---|---|
| PAC (LC-MS/MS): 8.3 ng/dL (230 pmol/L) | PAC (LC-MS/MS): 6.6 ng/dL (183 pmol/L) | K **3.3 mEq/L** | PAC (LC-MS/MS): 8.1 ng/dL (225 pmol/L) |
| PRA <0.6 ng/mL/h | PRA <0.6 ng/mL/h | | PRA <0.6 ng/mL/h |
| ARR >14 | ARR >11 | | ARR >14 |
| K 4.1 mEq/L | K 4.4 mEq/L | | K 4.3 mEq/L |

**Does this patient have primary aldosteronism?**

**Is further testing needed to make the diagnosis?**

Vaidya et al. NEJM 2025

# Case

36-y ...nts fo... ...om...

Age ...ecla... ...N

Low-Renin HTN
Renin-Independent
Aldosteronism

Low-Renin HTN
Renin-Independent
Aldosteronism

Hypokalemia
on ACEi?

Renin low on ACEi
ALDO not suppressed
on ACEi

Age 28 (CCB)
PAC (LC-MS/MS): 8.3 ng/dL
(230 pmol/L)
PRA <0.6 ng/mL/h
ARR >14
K 4.1 mEq/L

Age 32 (no meds)
PAC (LC-MS/MS): 6.6 ng/dL
(183 pmol/L)
PRA <0.6 ng/mL/h

Age 33 (CCB, ACEi)
K **3.3 mEq/L**

Age 36 (CCB, ACEi)
PAC (LC-MS/MS): 8.1 ng/dL
(225 pmol/L)
PRA <0.6 ng/mL/h
ARR >14
K 4.3 mEq/L

**Negative Confirmatory Test PA**
*(expert opinion)*

Oral Sodium Suppression Test:
24h UNa of 190 mEq
24h UAldo 9.7 mcg (>12)

Vaidya et al. NEJM 2025

# Case

36-year old woman presents for hypertension management

Age 27: 1st pregnancy, preeclampsia => Persistent HTN => nifedipine

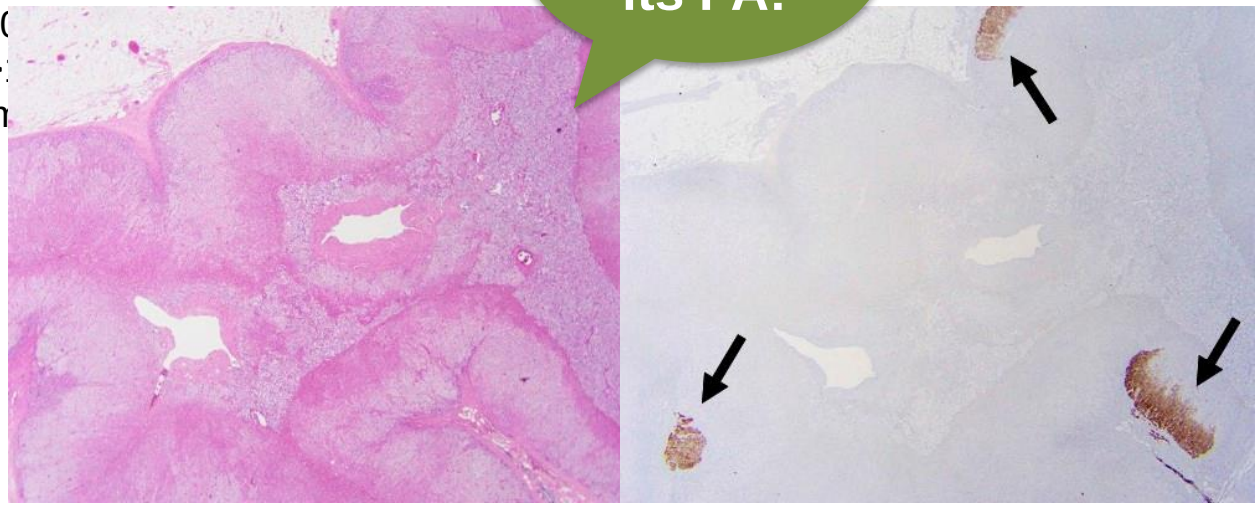
Age 28 (CCB)
PAC (LC-MS/MS): 8.3 ng/dL (230 pmol/L)
PRA <0.6 ng/mL/h
ARR >14
K 4.1 mEq/L

Age 32 (no meds)
PAC (LC-MS/MS): 6.6 ng/dL (183 pmol/L)
PRA <(
ARR >
K 4.4 m

Age 33 (C
K **3.3 m**

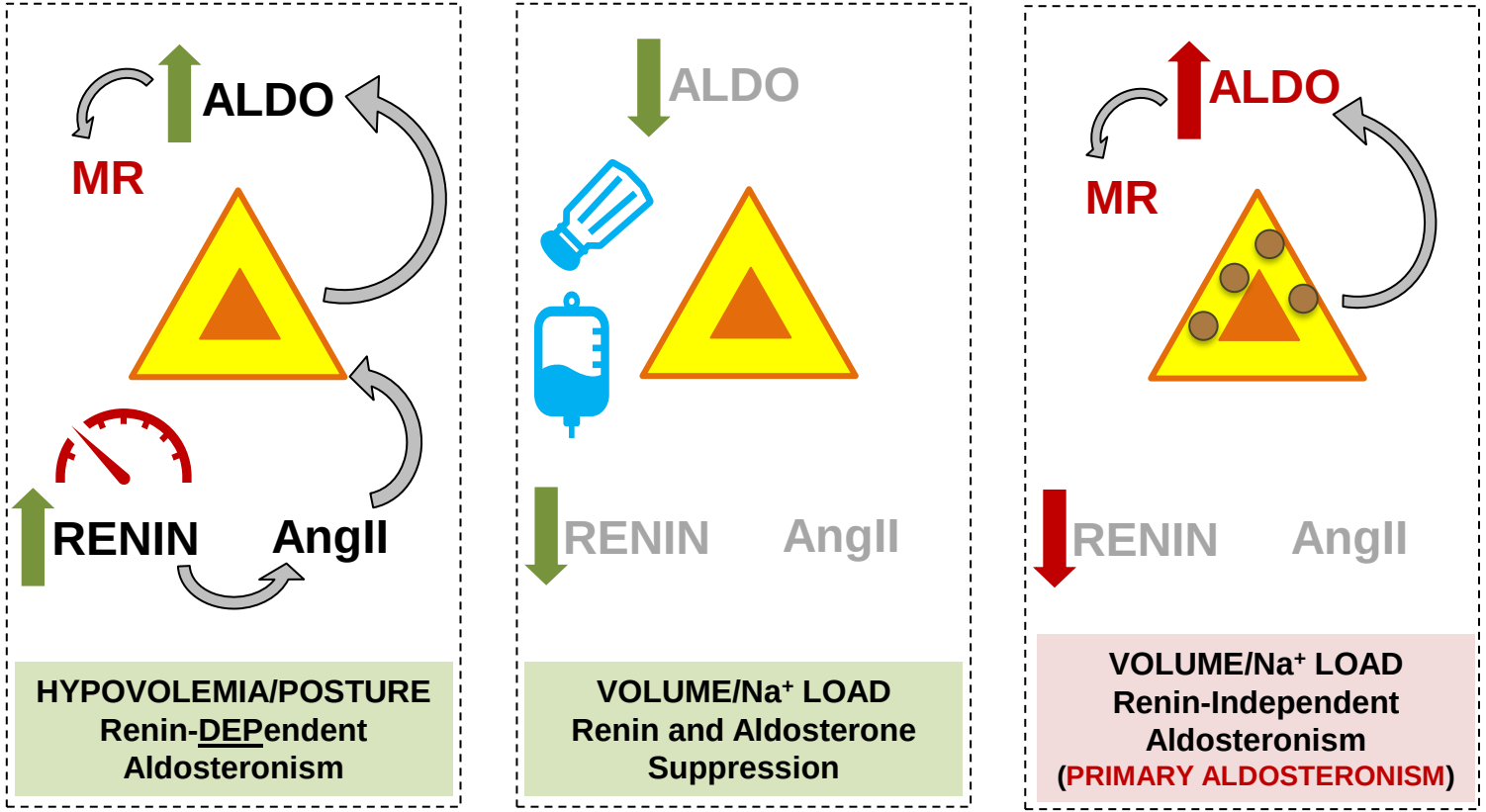
36 (CCB, **ACEi**)
C-MS/MS): 8.1 ng/dL (225 pmol/L)

Oral Sodium Suppression Test:
24h UNa of 190 mEq
24h UAldo 9.7 mcg (>12)




Vaidya et al. NEJM 2025

# Primary Aldosteronism



# What is Primary Aldosteronism?

**PATHOPHYSIOLOGIC SYNDROME:**

- Inappropriate aldosterone production: **renin-independent aldosterone production, relatively non-suppressible**
- Excessive activation of the MR, vicious cycle of volume expansion, hypertension, CV and Kidney disease *independent of BP*

**Clinical Manifestations:**

Most patients with PA **do not have** hypokalemia or Resistant HTN

**Hallmark Biochemical Diagnostics:**

*Suppression of Renin*

*Inappropriate/Dysregulated Production of Aldosterone*

Vaidya et al. Endocrine Reviews 2018

# Why should you care?

***Part I: Preventable Cardiovascular Risk***

*Part II: Under-recognition*

*Part III: High Prevalence*

# Risk for Incident Composite Cardiovascular Events

| | **Overt Primary Aldosteronism** (No Targeted Therapy) | **Matched Idiopathic Hypertension** |
|---|---|---|
| **CAD** | **~2x** | **-** |
| **Heart failure** | **~2x** | **-** |
| **Stroke** | **~2.5x** | **-** |
| **Afib** | **~3.5x** | **-** |
| **LVH** | **~2.3x** | **-** |

**↑CVD independent of BP**

Monticone et al, The Lancet D&E 2018

# Risk for Incident Composite Cardiovascular Events

## Why should you care?

*Part I: Preventable Cardiovascular Risk*

**Primary Aldosteronism increases the risk for CVD, CKD, and death…**

**…we have targeted therapies that can mitigate this risk**

Hundemer et al, The Lancet D&E 2018

# Why should you care?

*Part I: Preventable Cardiovascular Risk*

***Part II: Under-recognition***

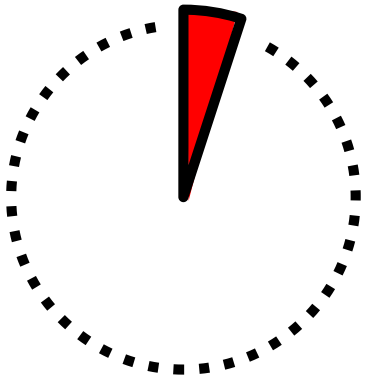
*Part III: High Prevalence*

# Failure to Screen for Primary Aldosteronism

## Recommended Indications to Screen

- Resistant HTN
- HTN + HypoK

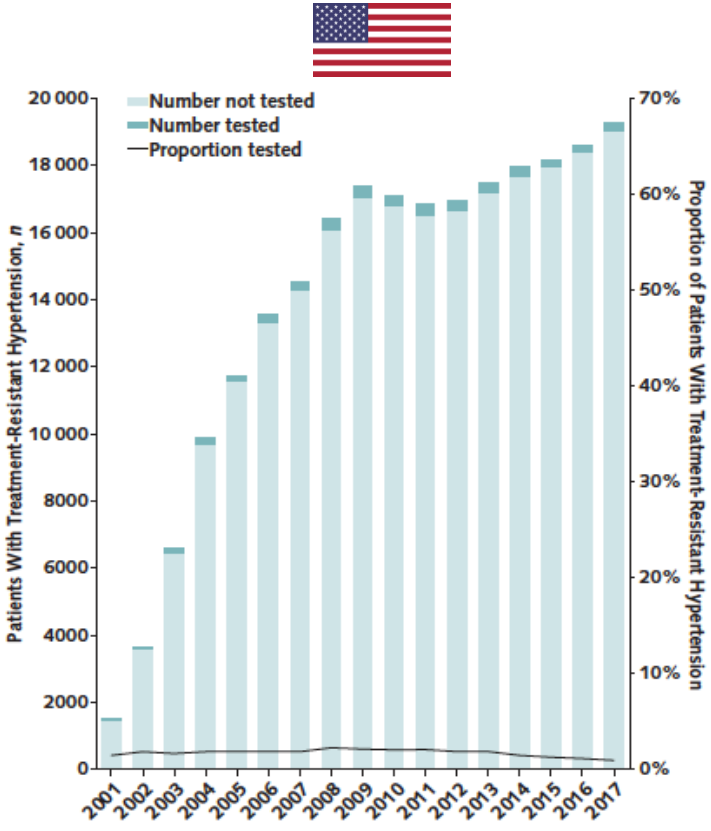
## Reality

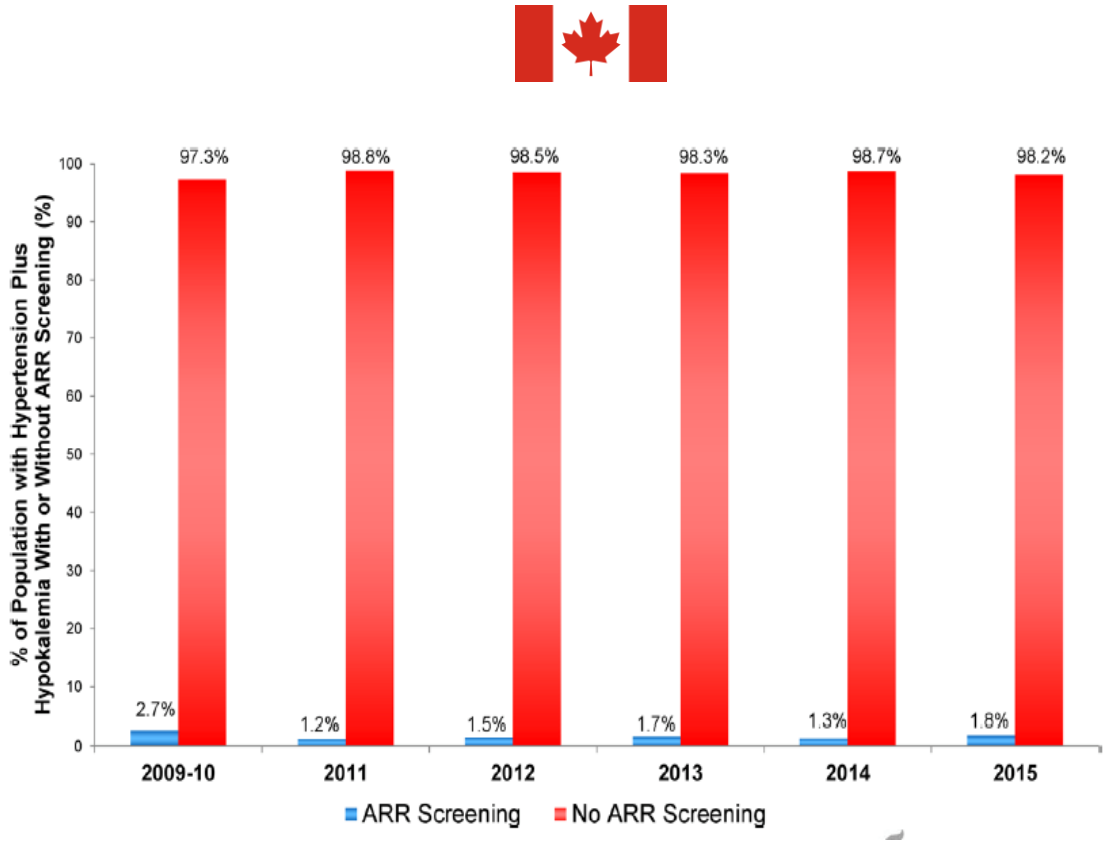


**<1-2% !!**

Burrello et al. Hypertension 2020; Ruhle et al. 2019; Jaffe et al. 2020; Cohen et al. 2021; Liu et al 2021; Hundemer et al. Hypertension 2021

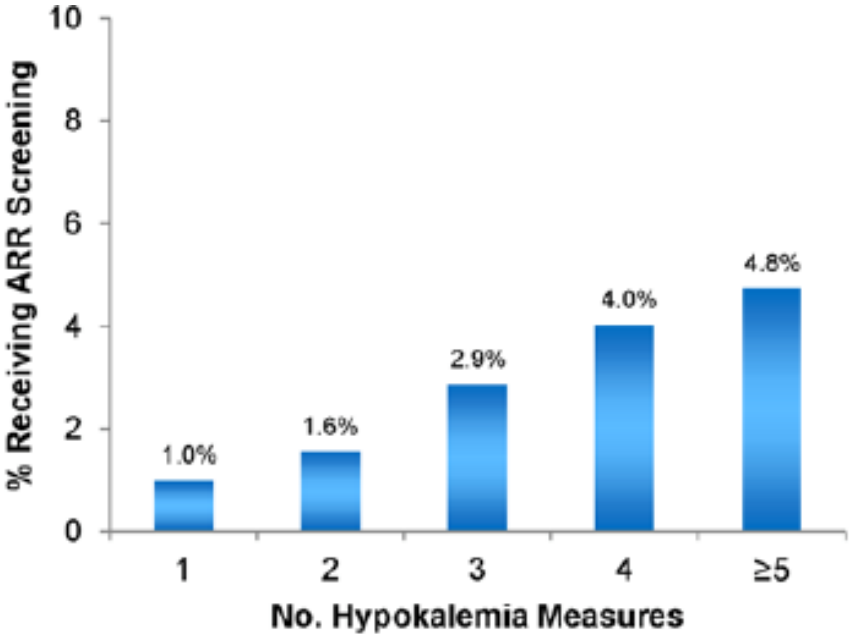
# Failure to Screen for Primary Aldosteronism

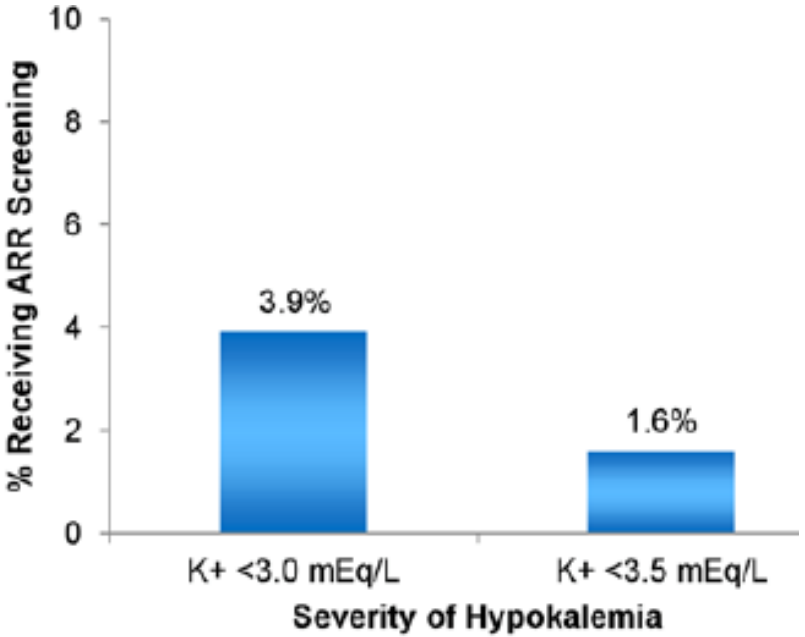



Burrello et al. Hypertension 2020; Ruhle et al. 2019; Jaffe et al. 2020; Cohen et al. 2021; Liu et al 2021; Hundemer et al. Hypertension 2021

# Failure to Screen for Primary Aldosteronism




Hundemer et al. Hypertension 2021

# Failure to Screen for Primary Aldosteronism

## Reasons Why PA is Under-Diagnosed

1) We don’t look for it!
2) When we do look for it, *we often mis-interpret or ignore the results*

# Why should you care?

*Part I: Preventable Cardiovascular Risk*

*Part II: Under-recognition*

***Part III: High Prevalence***

# Conservative Prevalence Estimates

| | |
|---|---|
| Resistant Hypertension | >25-30% |
| HTN + Hypokalemia | >30% |
| Stage I-II Hypertension | >15-20% |
| Pre-HTN/Normal BP | ~10% |

# Diagnostic Testing Complexity

**Key Point: The landscape of PA testing is dominated by *relatively arbitrary* and *unnecessarily complex* practices that rely on *unvalidated* diagnostic thresholds**

# Diagnostic Testing

***There is no reference/gold-standard diagnostic***
***Diagnostic thresholds are relatively arbitrary and not rigorously validated***

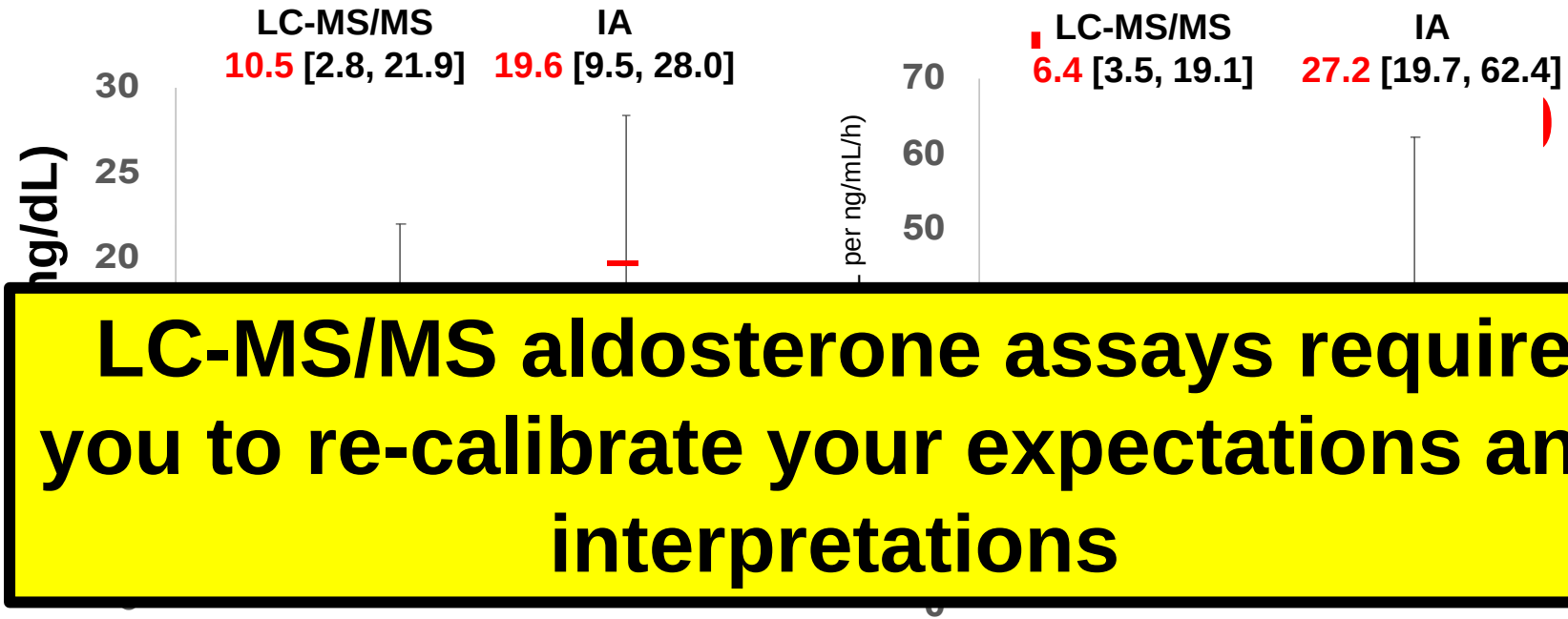
**ARR** ➡ **Relatively Arbitrary Thresholds**
**30, 25, 20, etc.**

**Aldosterone** ➡ **Relatively Arbitrary Thresholds**
**20, 15, 10 ng/dL, etc.**

**Aldosterone Suppression Tests** ➡ **Multiple Protocols**
**Arbitrary Thresholds**

# Aldosterone Assays

## Immunoassay → LC-MS/MS

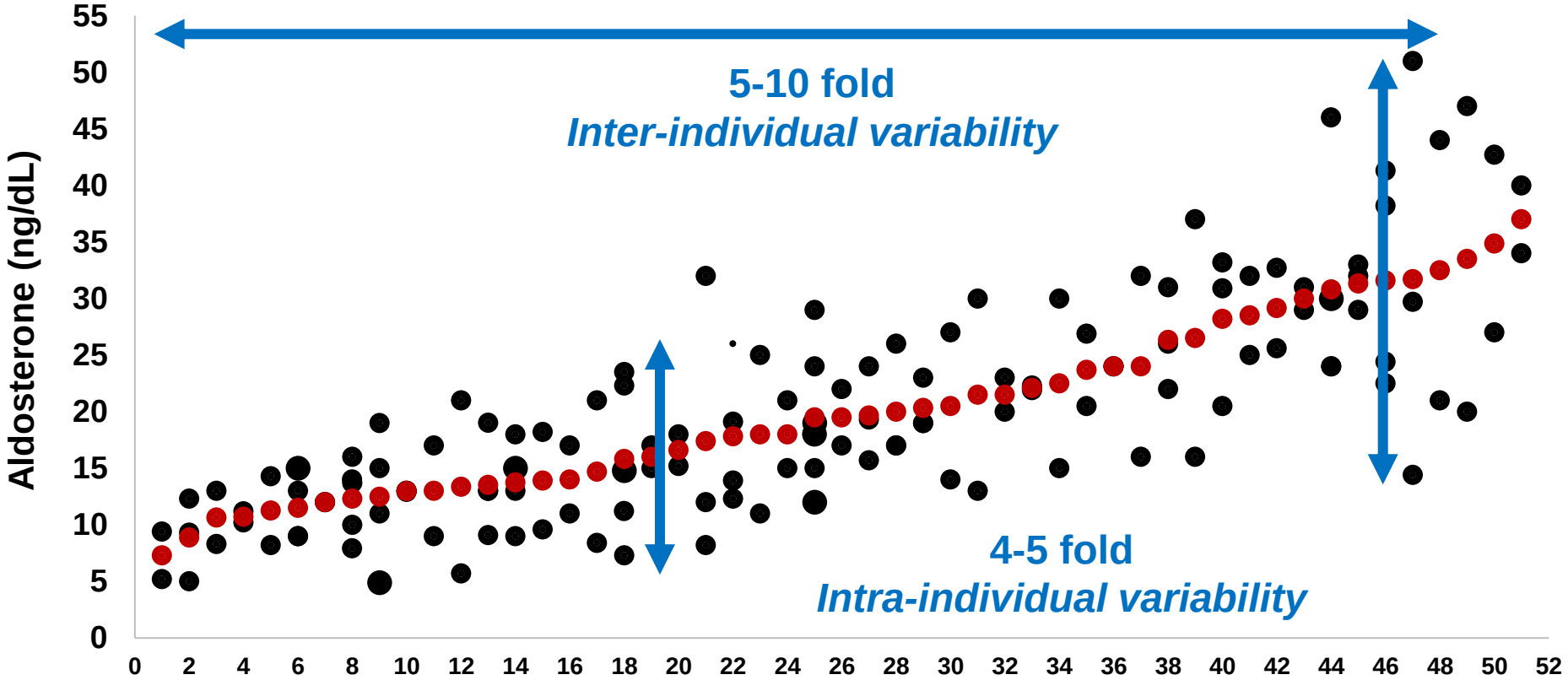



**LC-MS/MS aldosterone assays require you to re-calibrate your expectations and interpretations**

Brown et al. Journal of the Endocrine Soc 2022

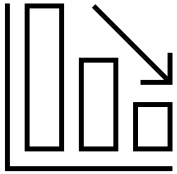
# Variability of Aldosterone Production

# Variability of Aldosterone Production




Yozamp et al. Hypertension 2021

# Variability of Aldosterone Production



**ALDO Thresholds**

< 15 ng/dL: **49%**

< 10 ng/dL: **29%**

**A single aldosterone measurement should not be used to confidently *exclude* the possibility of PA when the pre-test probability is high**

Yozamp et al. Hypertension 2021

# Continuum of Primary Aldosteronism

**Arbitrary/conventional diagnostic thresholds aside**

**How common is "*inappropriate, non-suppressible, renin-independent aldosterone production*"**
**(aka *Primary Aldosteronism Pathophysiology*)?**

**Aldosterone Suppression Test** → **Visualize the spectrum of PA**
***(agnostic of conventional thresholds)***

# Continuum of Primary Aldosteronism

**Oral Sodium Suppression Test**

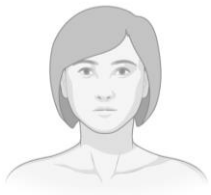
Brown et al. *Annals of Int Med* 2020

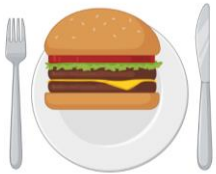
# Continuum of Primary Aldosteronism

## Oral Sodium Suppression Test

Supplemental $Na^+$ Intake

**~2-4 g/d x 3-4 days**





\+

Mean U.S. Dietary $Na^+$ Intake

**~3.5 g/d**

Net Summary

~4-6 g/d $Na^+$ x 3-4d
~1.5 L/d $H_2O$/NS x 3-4d

Physiologic Expectations

ECV/IVV Expansion
↓Renin
↓AngII
↓**Aldosterone**

Brown et al. *Annals of Int Med* 2020

# Continuum of Primary Aldosteronism


**CONTINUUM: severity spectrum of non-suppressible, renin/AngII-independent aldosterone production**

**This is physiologic**

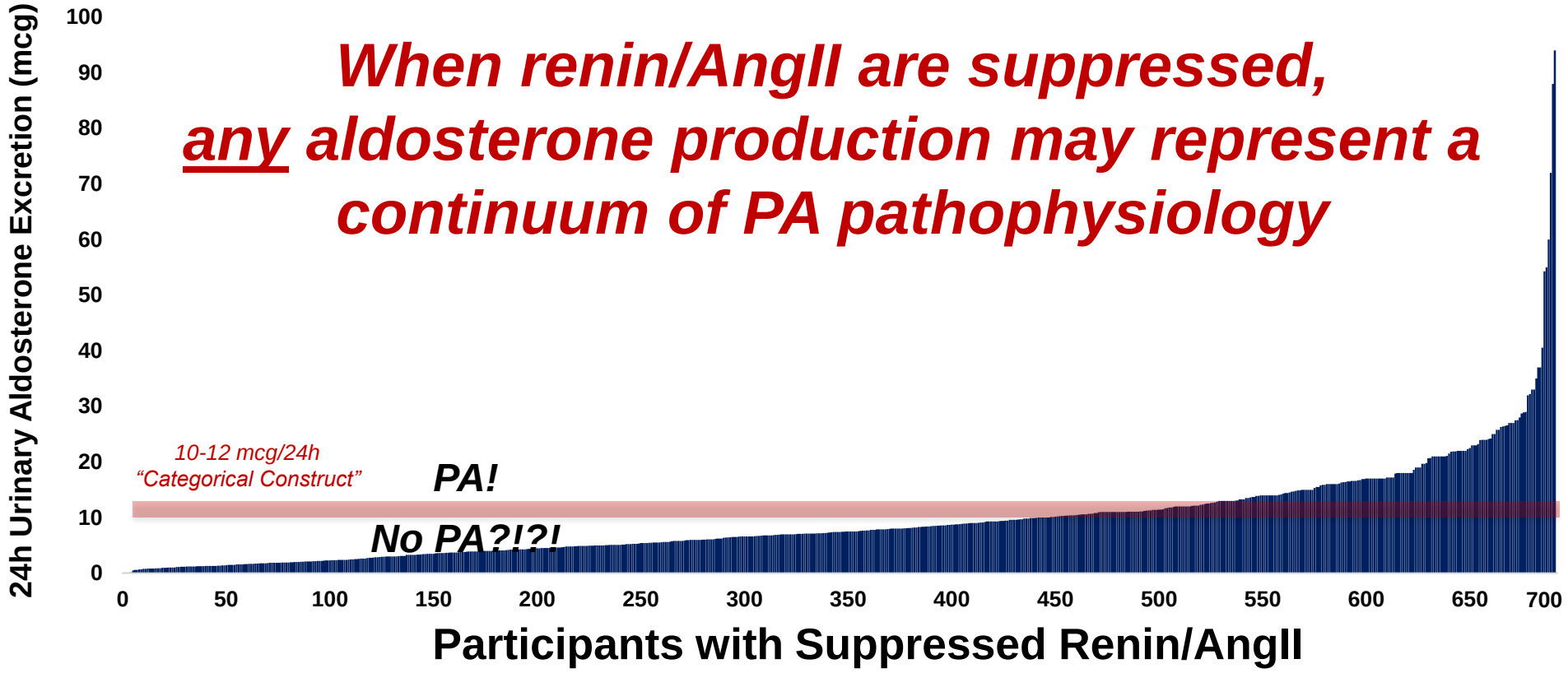
*When does physiology end?*
*When does pathophysiology begin?*

**This is pathophysiologic (aka overt PA)**

**Number of Participants with Suppressed Renin/AngII**

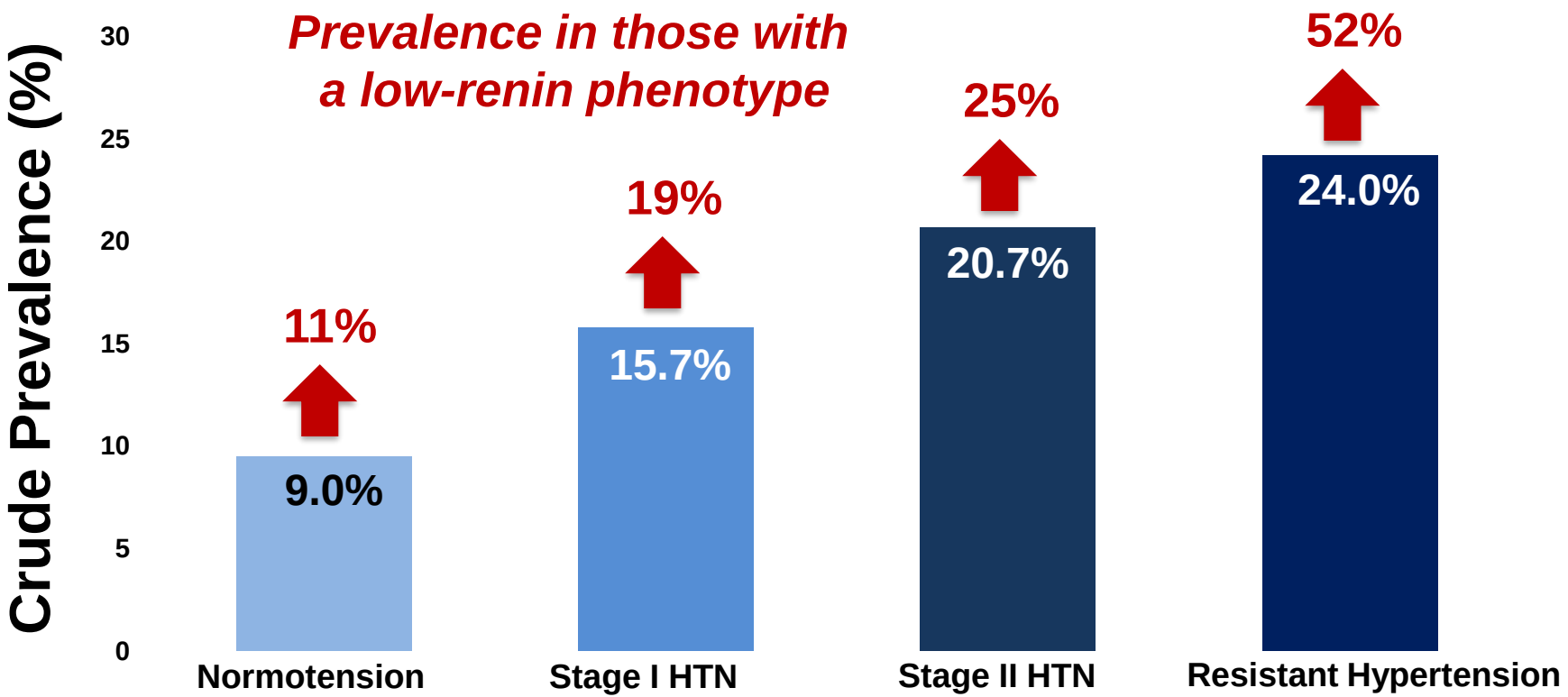
Brown et al. *Annals of Int Med* 2020

# Continuum of Primary Aldosteronism




Brown et al. *Annals of Int Med* 2020

# The Prevalence of Primary Aldosteronism




Brown et al. *Annals of Int Med* 2020

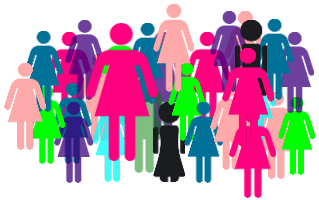
***Is the continuum of Primary Aldosteronism Pathophysiology clinically relevant?***

# Clinical Trials

**PATHWAY-2 trial : What is the best 4th drug for treat Resistant Hypertension?**

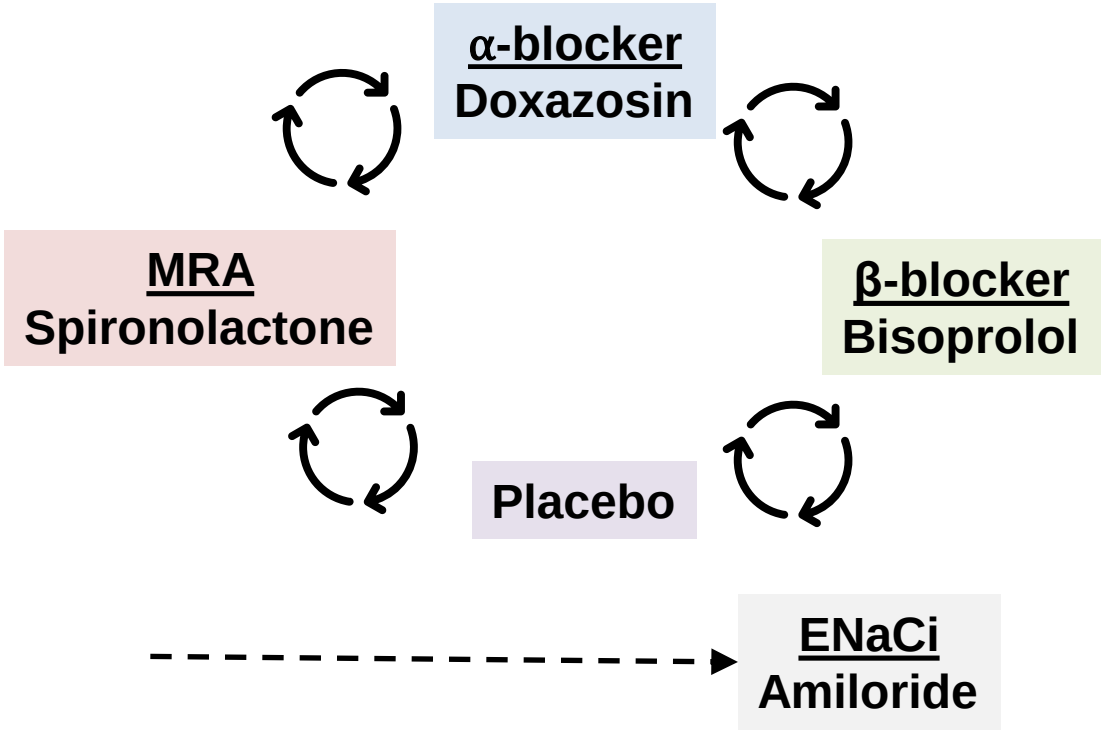
**Patients with R-HTN**

*(RAASi, diuretic, CCB)*



**“Secondary HTN excluded”**

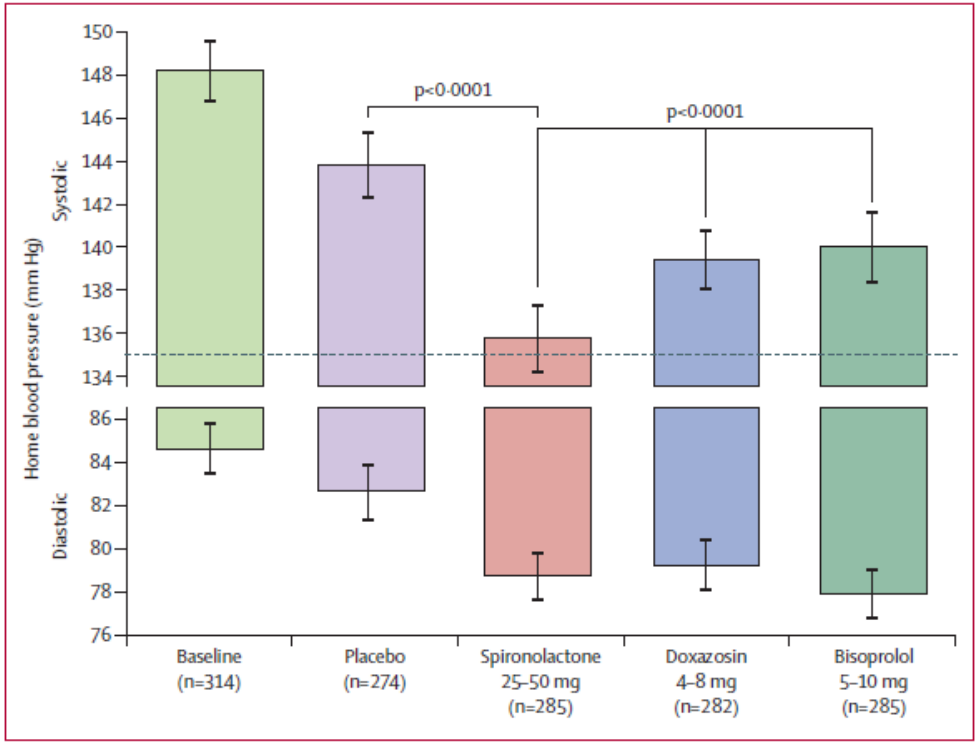
**Primary Aldosteronism [presumptively] excluded -**
***Aldo/ARR not “high enough”***




Williams et al. Lancet 2015

# Clinical Trials

## Best 4th Drug: MR Antagonist (& ENaCi)




Williams et al. Lancet 2015

# Clinical Trials

**This *IS* Primary Aldosteronism!**

**A substantial proportion of patients thought to have idiopathic resistant HTN have a form of renin-independent aldosteronism that is also MR-mediated and responsive to MRAs; however, the "traditional" approach to diagnosing primary aldosteronism misclassified this phenomenon**

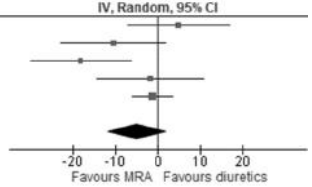
Williams et al. Lancet 2015 & Lancet D&E 2018

# Meta-Analysis of RCTs in LRH

## MRA vs Thiazides ( - 4.8 mmHg)

| Study or Subgroup | MRA Mean [mmHg] | MRA SD [mmHg] | MRA Total | Diuretic Mean [mmHg] | Diuretic SD [mmHg] | Diuretic Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Adlin | -24 | 15.8 | 18 | -29 | 15.1 | 10 | 17.8% | 5.00 [-6.87, 16.87] | 1972 |
| Vaughan | -28.3 | 17.8 | 21 | -17.9 | 19.7 | 16 | 17.2% | -10.40 [-22.69, 1.89] | 1973 |
| Spark | -32 | 11.4 | 10 | -13.9 | 15.3 | 10 | 17.9% | -18.10 [-29.93, -6.27] | 1974 |
| Ferguson | -13.1 | 15.1 | 11 | -11.4 | 15.1 | 11 | 16.8% | -1.70 [-14.32, 10.92] | 1977 |
| Hood (bendroflumethiazide) | -11.6 | 13.8 | 51 | -10.5 | 10.4 | 51 | 30.3% | -1.10 [-5.84, 3.64] | 2007 |
| Total (95% CI) | | | 111 | | | 98 | 100.0% | -4.75 [-11.91, 2.40] | |

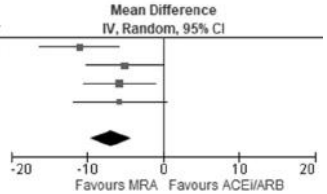
Heterogeneity: Tau² = 38.05; Chi² = 10.05, df = 4 (P = 0.04); I² = 60%
Test for overall effect: Z = 1.30 (P = 0.19)




## MRA vs ACEi/ARB ( - 6.8 mmHg)

| Study or Subgroup | MRA Mean [mmHg] | MRA SD [mmHg] | MRA Total | ACEi/ARB Mean [mmHg] | ACEi/ARB SD [mmHg] | ACEi/ARB Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Flack 2003 | -16 | 15.5 | 60 | -5 | 14.2 | 62 | 24.7% | -11.00 [-16.28, -5.72] | 2003 |
| Williams 2004 | -15.3 | 15.7 | 67 | -10.3 | 16 | 82 | 26.3% | -5.00 [-10.11, 0.11] | 2004 |
| Weinberger 2005 | -15.8 | 15.8 | 86 | -10.1 | 15.4 | 82 | 30.4% | -5.70 [-10.42, -0.98] | 2005 |
| Hood 2007 (losartan) | -11.6 | 13.8 | 51 | -5.9 | 17.7 | 51 | 18.5% | -5.70 [-11.86, 0.46] | 2007 |
| Total (95% CI) | | | 264 | | | 277 | 100.0% | -6.83 [-9.56, -4.10] | |

Heterogeneity: Tau² = 0.58; Chi² = 3.24, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 4.90 (P < 0.00001)




## MRA vs β-blocker ( - 4.5 mmHg)
## MRA vs α-blocker ( - 4.0 mmHg)

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial


ESC European Heart Journal - Cardiovascular Pharmacotherapy ORIGINAL ARTICLE

Spironolactone effect on the blood pressure of patients at risk of developing heart failure: an analysis from the HOMAGE trial

João Pedro Ferreira, Timothy Collier, Andrew L. Clark, Mamas A. Mamas, Hans-Peter Brunner-La Rocca, Stephane Heymans, Arantxa González, Fozia Z. Ahmed, Johannes Petutschnigg, Blerim Mujaj, Joe Cuthbert, Philippe Rouet, Pierpaolo Pellicori, Beatrice Mariottoni, Franco Cosmi, Frank Edelmann, Lutgarde Thijs, Jan A. Staessen, Mark Hazebroek, Job Verdonschot, Patrick Rossignol, Nicolas Girerd, John G. Cleland, and Faiez Zannad

Williams et al. Lancet 2015; Shah et al. JHH 2024

# KEY CONCEPT

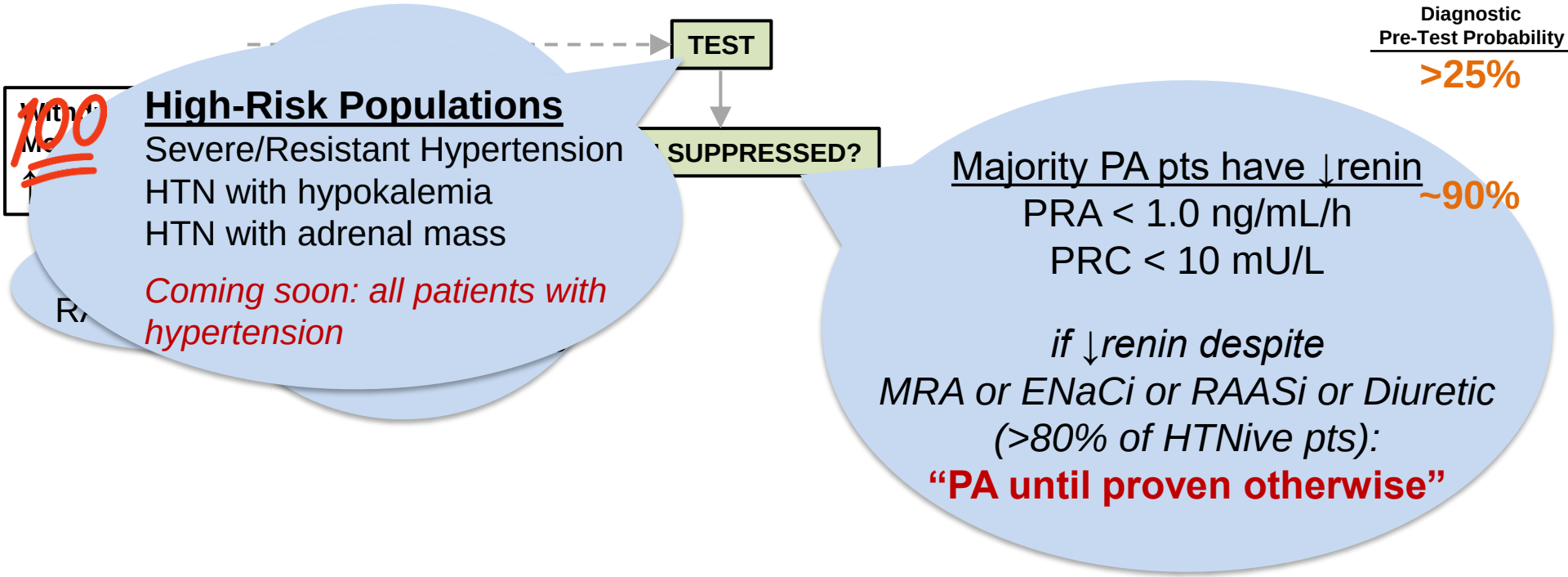
**Greater aldosterone production in the context of a low-renin phenotype is associated with progressive risk for CV and kidney disease and responds preferentially to MRA therapy**

**PA is a syndrome of pathophysiology characterized by *any* aldosterone production when renin is low; there is no lower limit of aldosterone that confidently excludes PA Pathophysiology**

# Re-Calibrating the Diagnostic Approach

**Adopting a new mindset…**

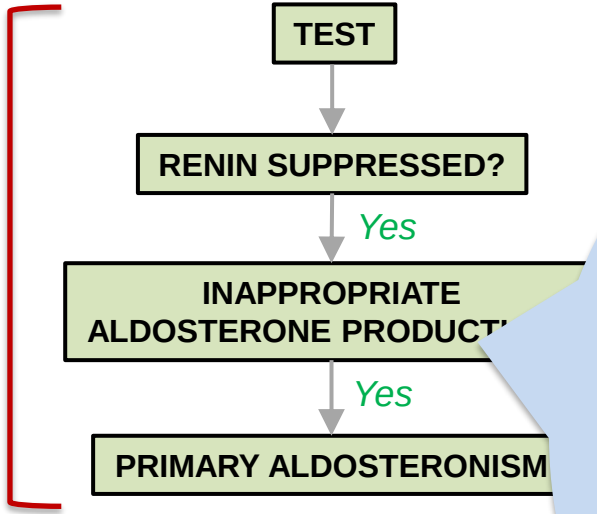
***"It's Primary Aldosteronism Until Proven Otherwise"***




Vaidya et al. NEJM 2025

Diagnostic
Pre-Test Probability
>25%

# CENTRAL DOGMA



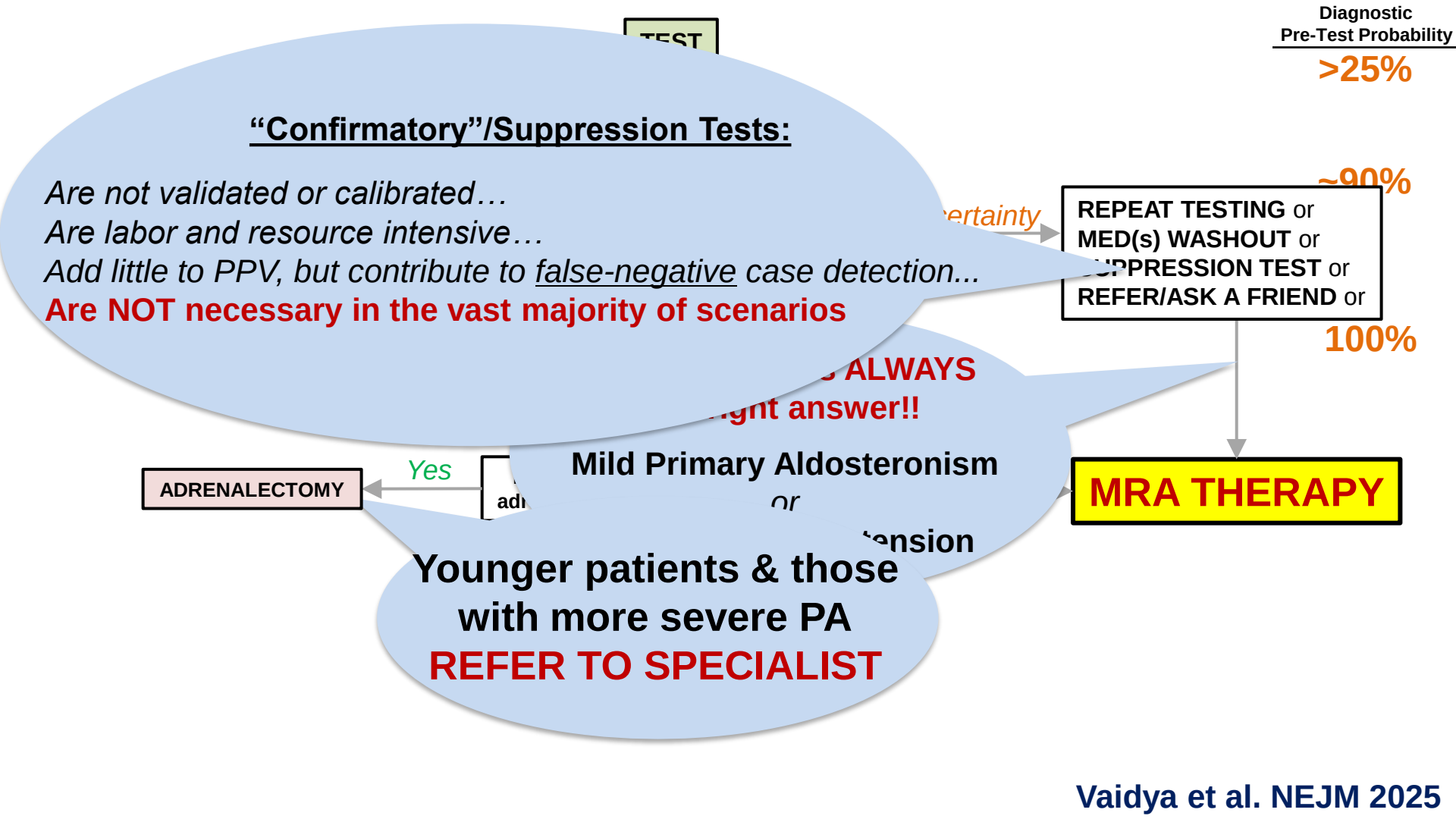

**Continuum**: *any aldosterone production when ↓renin represents PA pathophysiology amenable to targeted therapy*

**Categorical**: > XX ng/dL

*If on ACEi/ARB (75-80%):*
**"PA until proven otherwise"**

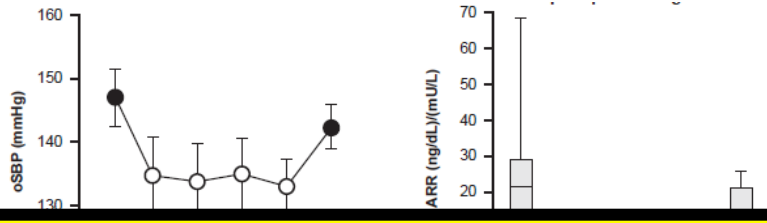
1. **Liberally test high-risk gro**
2. **Low or persistently suppresse highly indicative**
3. **Any inappropriate aldosterone production when renin is suppressed**

Vaidya et al. NEJM 2025




Vaidya et al. NEJM 2025

# Aldosterone Synthase Inhibitors


**ASIs appear to be a new anti-HTN class, highly effective at lowering aldosterone, and BP in R-HTN, uncontrolled HTN, and PA**

***They affirm that a large proportion of essential/idiopathic HTN is aldosterone-mediated***

# Adrenal Insufficiency

# Case

- 28yoF presents to ER 6 weeks after having a baby
- Cannot breastfeed well
- Presents with progressive fatigue, dizziness, orthostasis, salt craving, hyperpigmentation, anorexia, and weight loss
- BP=60/40 mmHg
- IV saline (8L) and BP improves

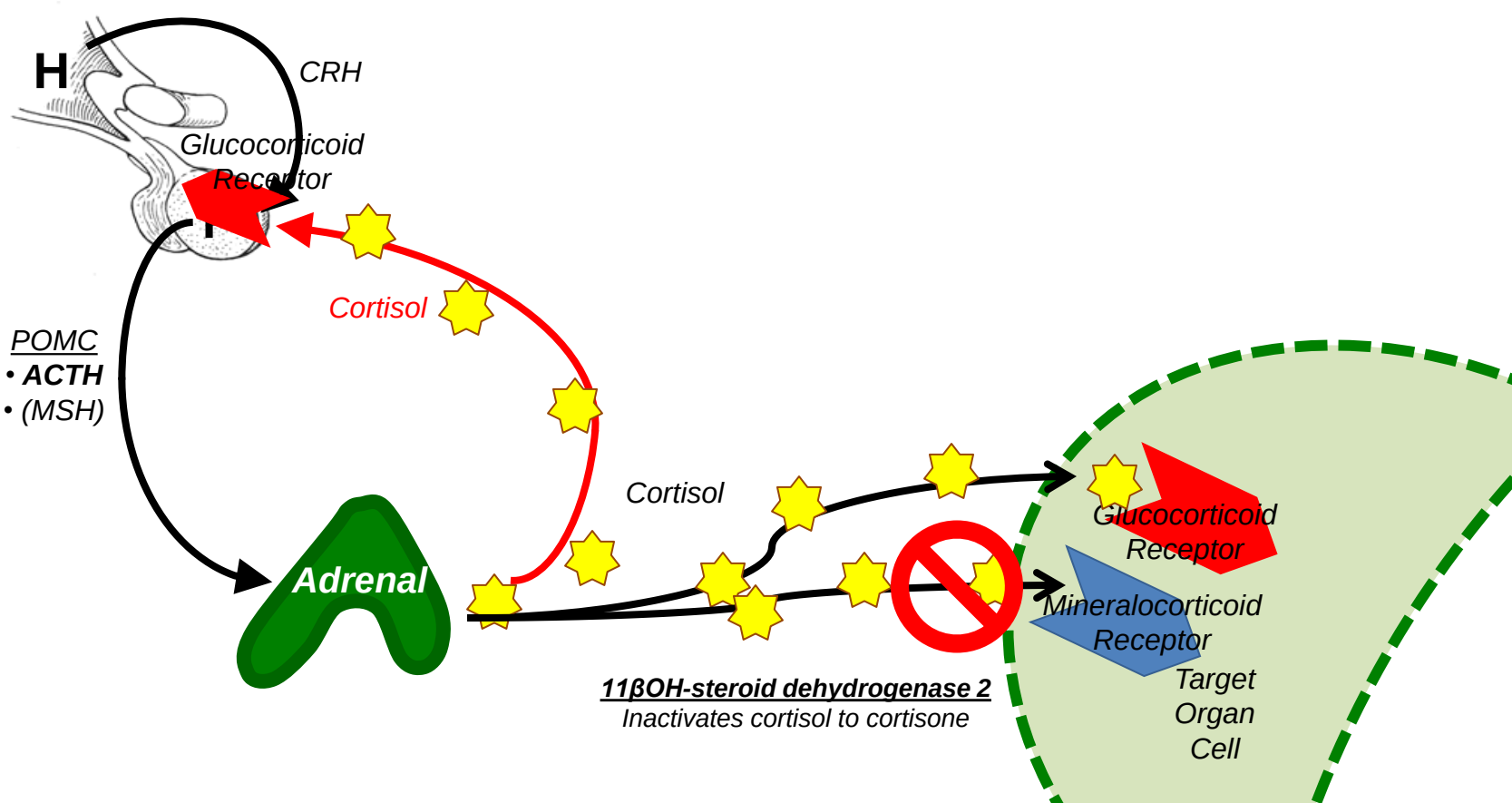
- Cortisol 0.80 mcg/dL (3-21)
- ACTH>1000pg/mL (15-75)
- (60mins after 250 mcg cosyntropin)= 1.0 mcg/dL

# Question

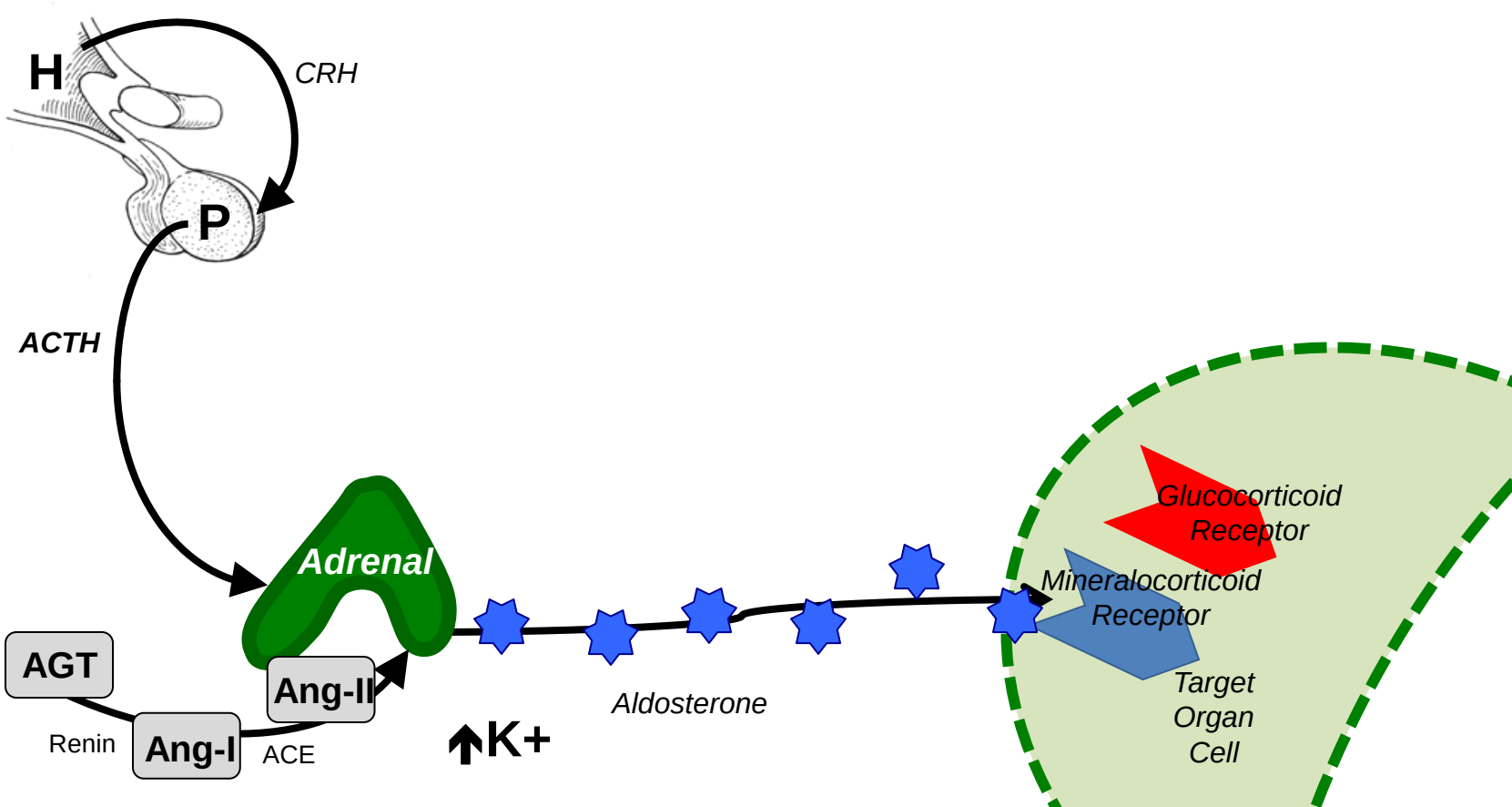
**The most likely diagnosis is:**

A) **Primary adrenal insufficiency**
B) Acute secondary adrenal insufficiency
C) Chronic secondary adrenal insufficiency
D) Ectopic ACTH syndrome
E) Cushing’s disease

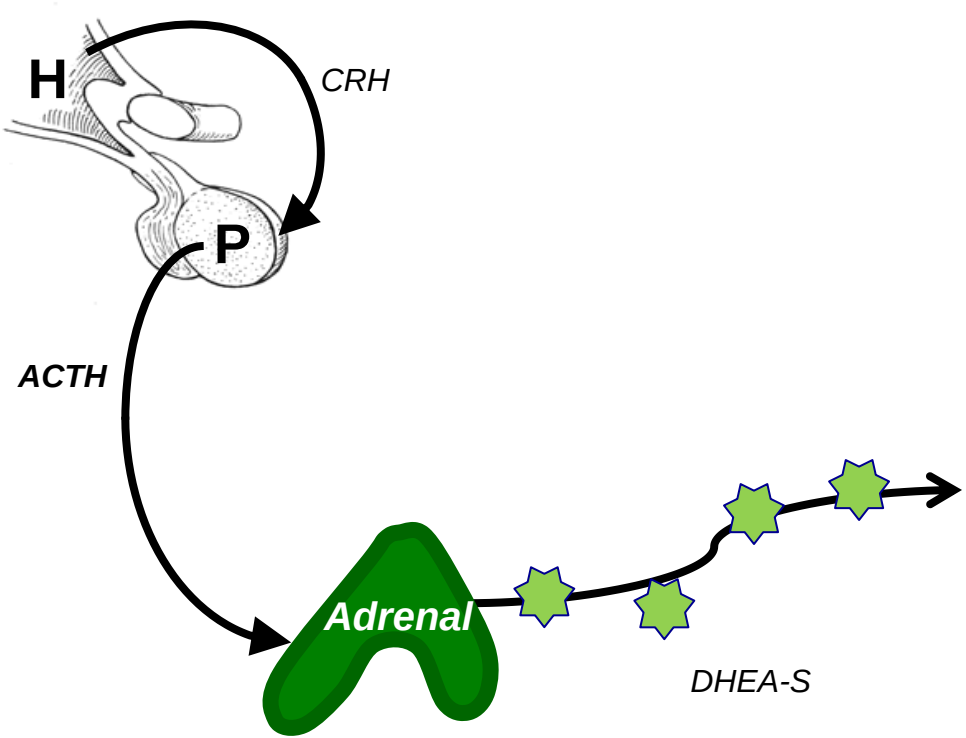
# Hypothalamic-Pituitary-Adrenal Physiology

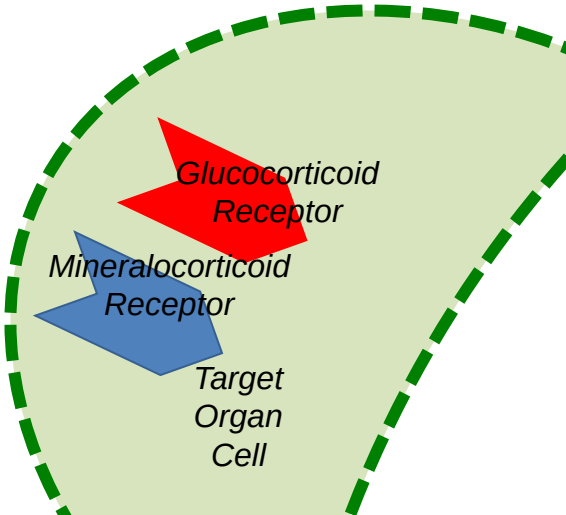


# Hypothalamic-Pituitary-Adrenal Physiology



# Hypothalamic-Pituitary-Adrenal Physiology



# Hypothalamic-Pituitary-Adrenal Physiology

1) **Cortisol and DHEA production are entirely dependent on ACTH; they are low in <u>every</u> form of adrenal insufficiency**

   DHEA-S is the sulfated, stable, long-acting metabolite of DHEA

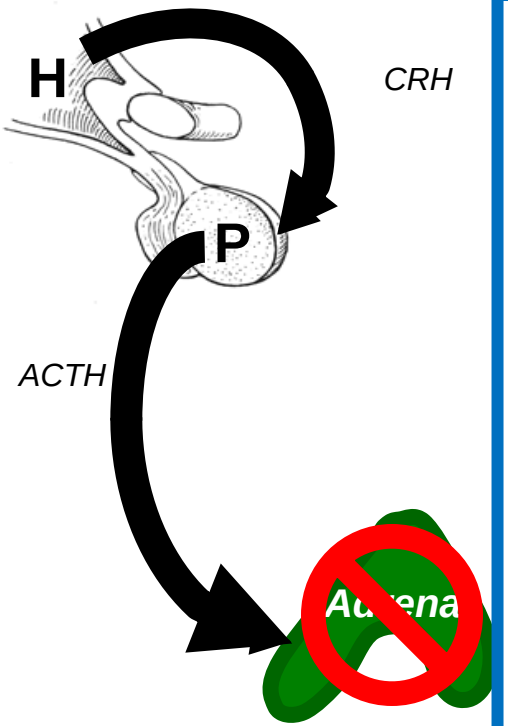
**2) Aldosterone is not dependent on ACTH. It is regulated in part by:**

- Angiotensin II (Renin-angiotensin system)
- $K^+$ balance
- ACTH

**3) HPA axis responds to:**

- Diurnal variation/clock
- "stress": ACTH & cortisol secretion is augmented "relative" to the degree of stress

# Primary Adrenal Insufficiency
## *(Addison's Disease)*

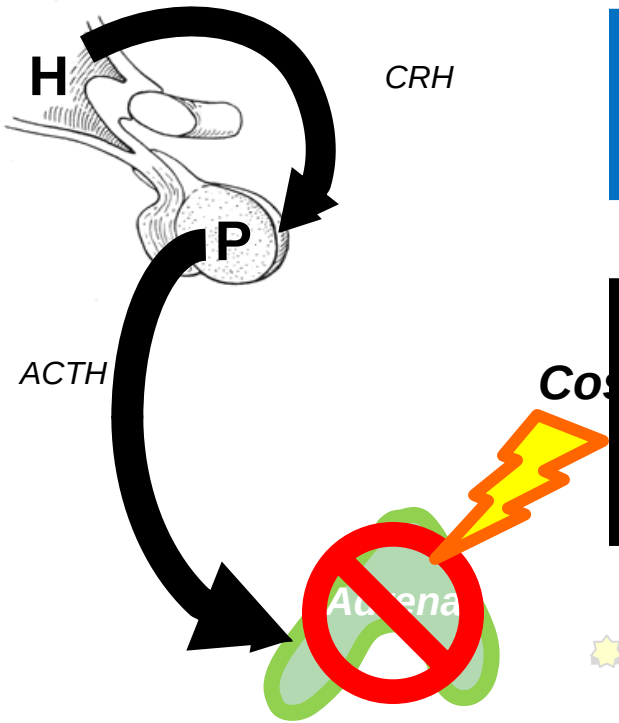



Manifestations/Characteristics:

*Labs:*
- low cortisol & DHEAS
- high ACTH
- low aldosterone
  - -hyperkalemia, hyponatremia, hypovolemia

*Physical Exam:*
- fatigue/lethargy/anorexia
- hypotension/orthostasis/salt craving
- weight loss
- hyperpigmentation
- abdominal pain
- many many more

# Primary Adrenal Insufficiency
## *(Addison's Disease)*

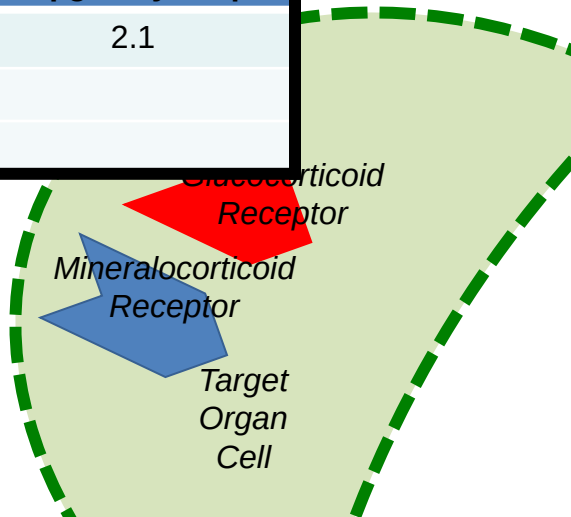



Response to Cosyntropin:

- sub-optimal

***EXAMPLE:***

| | Morning | 60 mins following 250 µg cosyntropin |
|---|---|---|
| **Cortisol** (µg/dL) | 1.8 ↓ | 2.1 |
| **ACTH** (pg/mL) | 1100 ↑ | |
| **DHEAS** (mcg/mL) | 33 ↓ | |



# Primary Adrenal Insufficiency (Addison's)

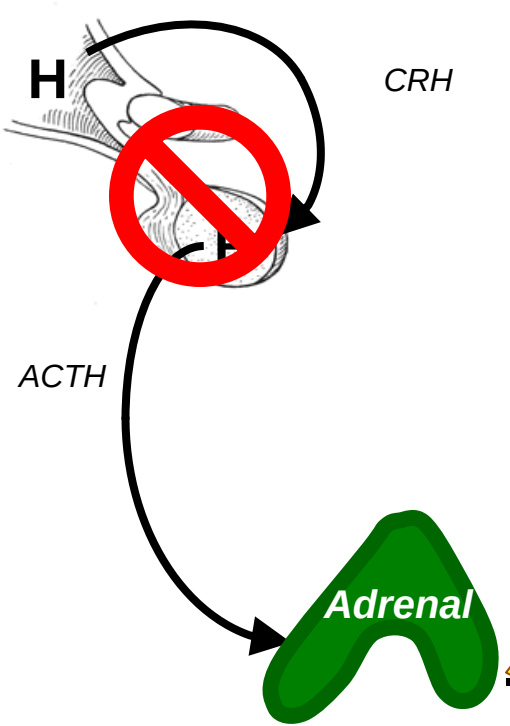
## Causes:

- Autoimmune
- Infiltrative infections (TB, fungal)
- Hemorrhage
- Infiltrative malignancy
- Congenital adrenal hyperplasia
- adrenoleukodystrophy

## Medications:

- Anti-fungal medications
- Immunotherapies
- Heparin
- Etomidate

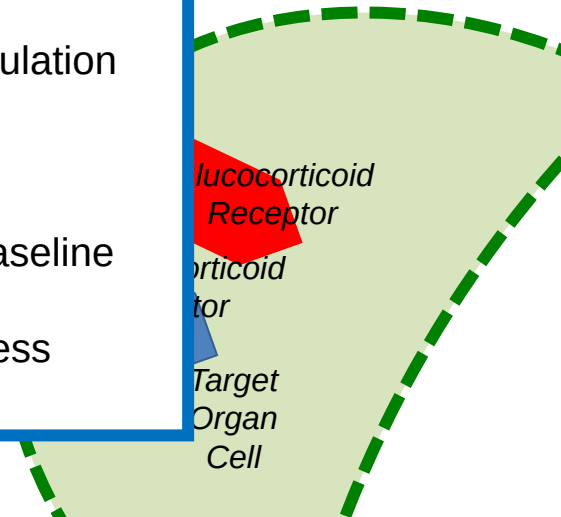
# *ACUTE* Secondary Adrenal Insufficiency



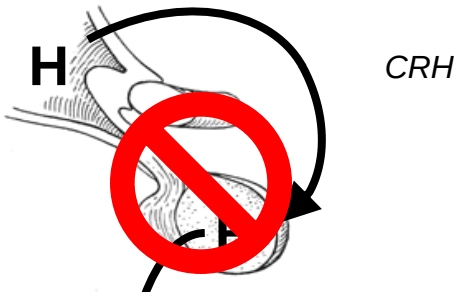

Manifestations/Characteristics:

*Labs:*
- low basal cortisol & DHEAS
- inappropriately low ACTH
- ± hyponatremia
- Normal K and aldosterone regulation

*Physical:*
- completely normal
- mild, progressive, fatigue at baseline
- severe fatigue, orthostasis, hypotension, in situations of stress



# *ACUTE* Secondary Adrenal Insufficiency

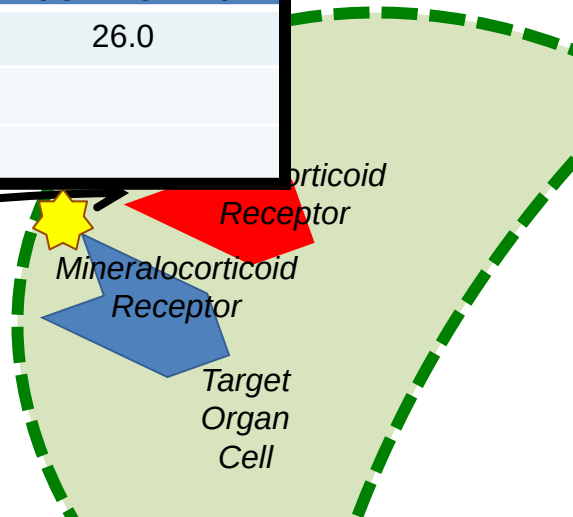



Response to Cosyntropin:

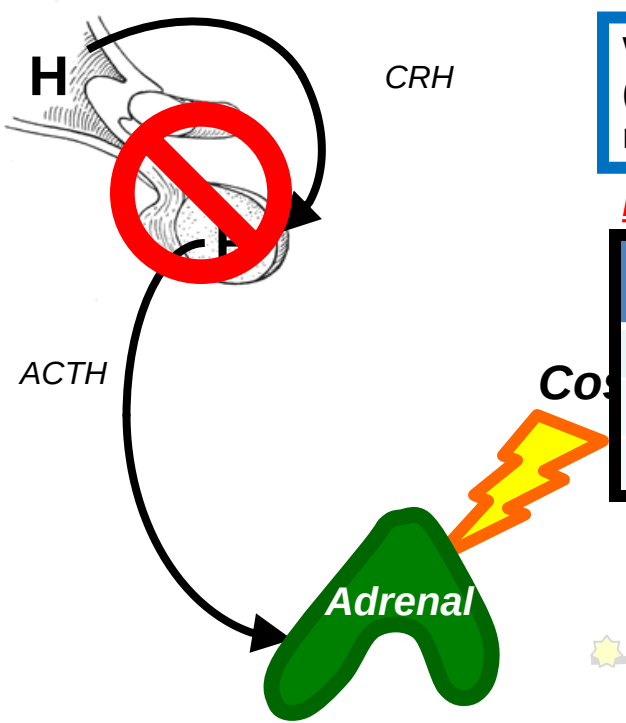
- NORMAL

***EXAMPLE:***

| | Morning | 60 mins following 250 µg cosyntropin |
|---|---|---|
| **Cortisol** (µg/dL) | 2.2 ↓ | 26.0 |
| **ACTH** (pg/mL) | 10 ↓ | |
| **DHEAS** (mcg/mL) | 38 ↓ | |



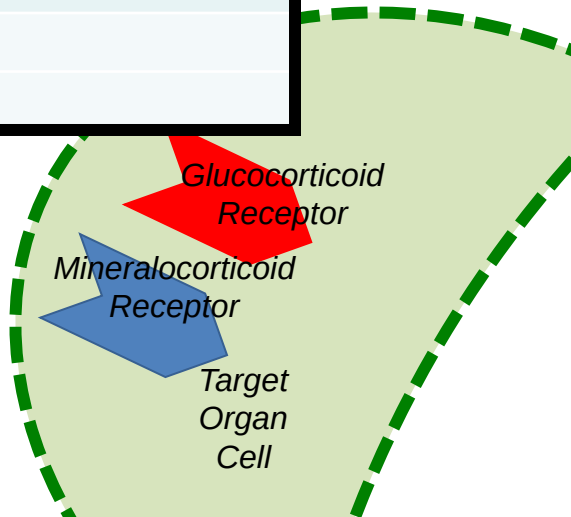
# *CHRONIC* Secondary Adrenal Insufficiency




With chronic ACTH deficiency, **adrenal cortex (ZF) will atrophy**, and will progressively respond less to cosyntropin stimulation

***EXAMPLE:***

| | Morning | 60 mins following 250 µg cosyntropin |
|---|---|---|
| **Cortisol** (µg/dL) | 2.2 ↓ | 4.5 |
| **ACTH** (pg/mL) | 10 ↓ | |
| **DHEAS** (mcg/mL) | 38 ↓ | |



# Secondary Adrenal Insufficiency

**Causes:**

- Pituitary mass: adenoma or metastatic lesion
- Pituitary infection
- Pituitary infiltration (granulomatous disease, iron)
- Pituitary trauma

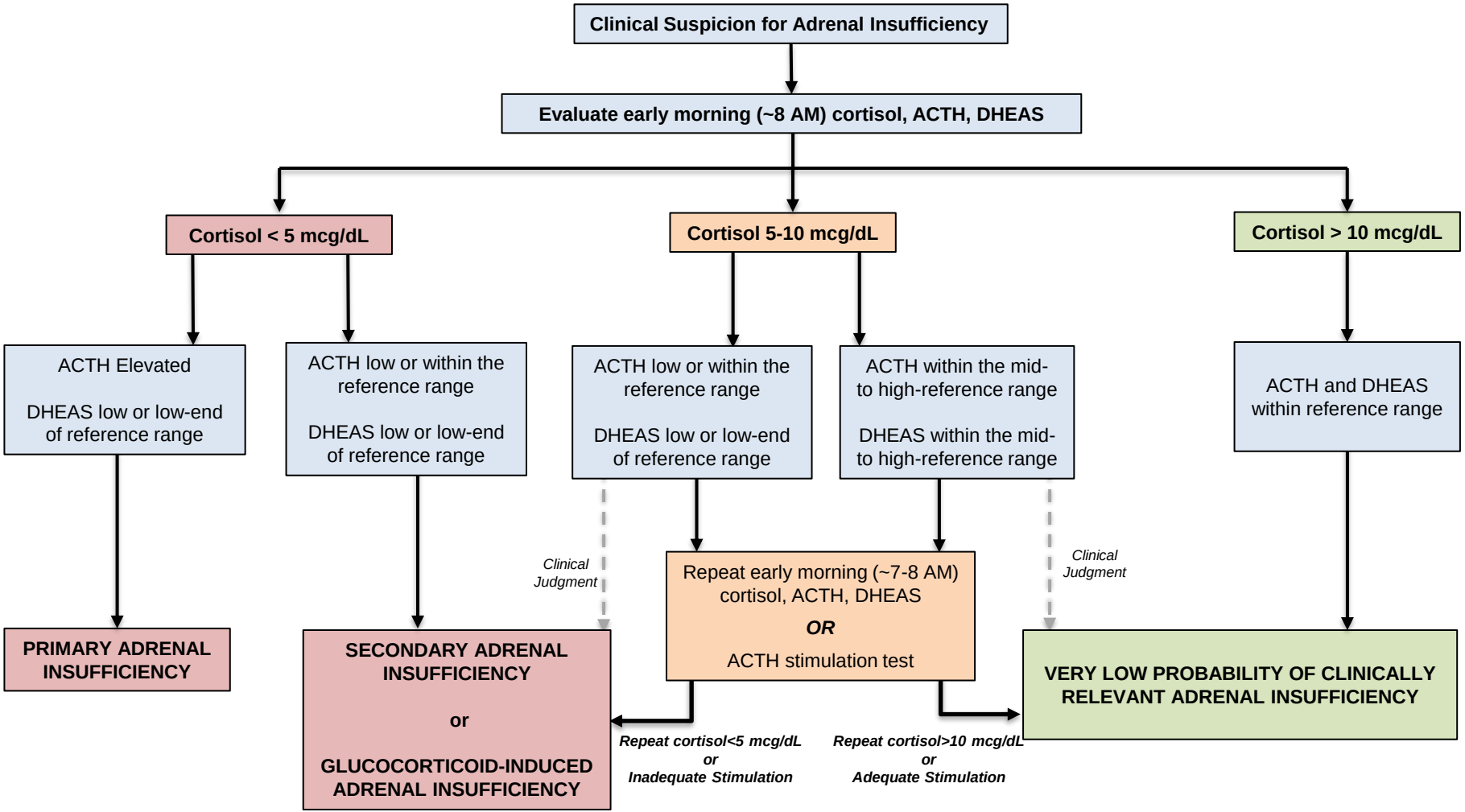
Medications:

- **Glucocorticoids (oral, inhaled, nasal, intra-articular)**

**Glucocorticoid-induced adrenal insufficiency (iatrogenic) is common**

# Glucocorticoid-Induced Adrenal Insufficiency

- **Common** (1-3% of adults are prescribed glucocorticoids at some point in their life)
- Supra-physiologic dosing for >3 weeks can induce GIAI (e.g. prednisone >5mg per day for >3 weeks)
- Can be induced by non-oral formulations (inhaled, intranasal, intraarticular, topical)
- Can be reversed with gradual tapering of glucocorticoids to demonstrate normal cortisol and HPA axis function




Vaidya et al. *JAMA* 2025

# Adrenal Crisis

Hemodynamic instability or shock due to cortisol deficiency

All patients with AI should be educated on the risk of adrenal crisis during periods of illness (fevers, vomiting, etc), trauma, or surgical procedures

Additional oral glucocorticoid therapy should be prescribed to match the insult; if oral therapy cannot be taken, IM or IV therapy is required

All patients should be prescribed and taught to administer IM glucocorticoid for emergencies

# Adrenal Crisis

https://doi.org/10.1093/ejendo/lvae029

**Table 8:** Suggested glucocorticoid regimens in patients at risk of or with diagnosed glucocorticoid-induced adrenal insufficiency during exposure to stress

| | General considerations | Examples | Suggested regimen |
|---|---|---|---|
| **Minor stress** | If the patient is already taking hydrocortisone ≥40 mg daily prednisone ≥10 mg daily, or dexamethasone ≥1 mg daily, there is typically no need to increase the dose unless there are signs of hemodynamic instability. | • Illness requiring bed rest<br>• Illness with fever (out of hospital)<br>• Illness requiring treatment with antibiotics (out of hospital)<br>• Significant emotional stress (e.g., bereavement) | If not on daily glucocorticoids: give hydrocortisone 40 mg total daily dose, to be given in three divided doses (e.g., 20 mg on rising, 10 mg 12 midday, 10 mg 5pm). Continue for 2-5 days until well (or for the duration of antibiotic treatment).<br>If on hydrocortisone <40 mg total daily dose: increase to 40 mg total daily dose, to be given in three divided doses (e.g., 20 mg on rising, 10 mg 12 midday, 10 mg 5pm). Continue for 2-5 days until well (or for the duration of antibiotic treatment).<br>If on prednisone <10 mg total daily dose: increase to 10 mg total daily dose, to be given in one or two divided doses. Continue for 2-5 days until well (or for the duration of antibiotic treatment).<br>If on dexamethasone <1 mg total daily dose: increase to 1 mg once daily. Continue for 2-5 days until well. |
| | | Minor surgery including any procedure requiring local anesthesia | If not on daily glucocorticoids: give oral hydrocortisone 40 mg total daily dose, to be given in three divided doses (e.g., 20 mg one hour prior to the procedure, 10 mg six hours after the procedure, 10 mg after a further six hours). Continue glucocorticoids in patients who remain unwell after the procedure until clinically stable.<br>If on hydrocortisone <40 mg total daily dose: increase to 40 mg total daily dose, to be given in three divided doses (e.g., 20 mg one hour prior to the procedure, 10 mg six hours after the procedure, 10 mg after a further six hours). Continue increased dose in patients who remain unwell after the procedure until clinically stable.<br>If on prednisone <10 mg total daily dose: increase to 10 mg total daily dose, to be given one hour prior to the procedure. Continue increased dose in patients who remain unwell after the procedure until clinically stable.<br>If on dexamethasone <1 mg total daily dose: increase to 1 mg total daily dose, to be given one hour prior to the procedure. Continue increased dose in patients who remain unwell after the procedure until clinically stable. |
| | | Bowel procedures not carried out under general anesthesia | If not on daily glucocorticoids: give hydrocortisone 20 mg total daily dose, to be given in three divided doses (e.g., 10 mg one hour prior to the procedure, 5 mg six hours after the procedure, 5 mg after a further six hours).<br>If on daily glucocorticoids: continue normal glucocorticoid dose. Give an equivalent I.V. dose if prolonged nil by mouth. |
| **Moderate and major stress** | If the patient is already taking hydrocortisone ≥200 mg daily, prednisone ≥50 mg daily, or dexamethasone ≥6-8 mg daily, there is typically no need to increase the dose<br>In patients with suspected reduced absorption (persistent vomiting or diarrhea), nil by mouth, or unable to take | Severe intercurrent illness, for example:<br>• Persistent vomiting or diarrhea from gastro-intestinal illness.<br>• Infection requiring hospital admission or I.V. antibiotics (e.g., sepsis). | For patients with persistent vomiting or diarrhea who are well enough to remain out of hospital: Hydrocortisone 100 mg I.M. injection immediately, which can be repeated after 6 hours if needed. If symptoms do not resolve or hemodynamic instability develops, admit to hospital for I.V. urgent |

# Incidentally Discovered Adrenal Masses

# Adrenal Tumors

Adrenal tumors are incidentally discovered in 1-10% of adults who are scanned.

A minority represent malignant entities (primary adrenal malignancy or extra-adrenal metastasis)

In contrast, ~10-25% of adrenal tumors autonomously secrete adrenal hormones. These “functional” tumors are associated with an increased risk for cardiometabolic outcomes, such as CV disease, diabetes, and osteoporosis/fracture.

Therefore, all incidentally discovered adrenal tumors should be carefully evaluated to determine whether they are: 1) **malignant** and/or 2) **functional**.

# Differential Diagnosis of Adrenal Mass

| | NON-FUNCTIONAL (85-95%) | FUNCTIONAL (5-15%) |
|---|---|---|
| **BENIGN (~90-95%)** | **Adrenocortical Adenoma**<br>Cyst<br>Ganglioneuroma<br>Hemangioma<br>Hemorrhage<br>Infections and granulomatous disease (tuberculosis, fungi, sarcoidosis)<br>Lymphangioma<br>Myelolipoma<br>Pheochromocytoma<br>Schwannoma | **Adrenocortical Adenoma**<br>*Aldosterone producing*<br>*Cortisol producing*<br>Micro- or Macro-nodular Disease<br>*Aldosterone producing*<br>*Cortisol producing*<br>Pheochromocytoma<br><br>Myelolipoma*<br>Ganglioneuroma* |
| **MALIGNANT (~5%)** | Adrenocortical carcinoma<br>Metastatic cancer from a non-adrenal primary<br>Neuroblastoma | Adrenocortical carcinoma<br>Pheochromocytoma |

# Radiographic Characteristics

| Characteristics | Likely Benign | Potentially Malignant |
|---|---|---|
| **Irregular Shape** | No | Yes |
| **Heterogeneous content** | No | Yes |
| **Necrosis or Calcifications** | No | Yes |
| **Rate of Growth** | < 1cm/y | ≥1cm/y |
| **Attenuation on unenhanced CT** | <10 HU | ≥ 20 HU |
| **Contrast washout on CT protocol at 15 minutes** | Absolute>60%<br>Relative>40% | Absolute ≤60%<br>Relative ≤40% |
| **MRI chemical shift suggestive of lipid-rich content** | Yes | No |
| **FDG avidity on PET** | No | Yes |
| **Size** | < 4 cm | ≥ 4-6 cm |

# Biochemical Testing

*Suggested **<u>screening biochemical evaluation</u>** for adrenal masses:*

| Condition | Patients | Test | Abnormal Value |
|---|---|---|---|
| **Hypercortisolism** | **ALL** | 1 mg Dexamethasone Suppression Test | None: ≤1.8 mcg/dL<br>MACS: 1.9-5.0 mcg/dL<br>ACS: > 5.0 mcg/dL |
| **Primary Aldosteronism** | HTN and/or hypokalemia | Ser<br>to p<br>acti | |
| **Pheochromocytoma** | Lipid poor, contrast avid, heterogeneous adrenal masses | Plas<br>frac<br>metanephrin | |
| **Adrenal androgen excess** | Hirsutism or virilization | DHEAS<br>Total Testosterone | Higher than ULN |

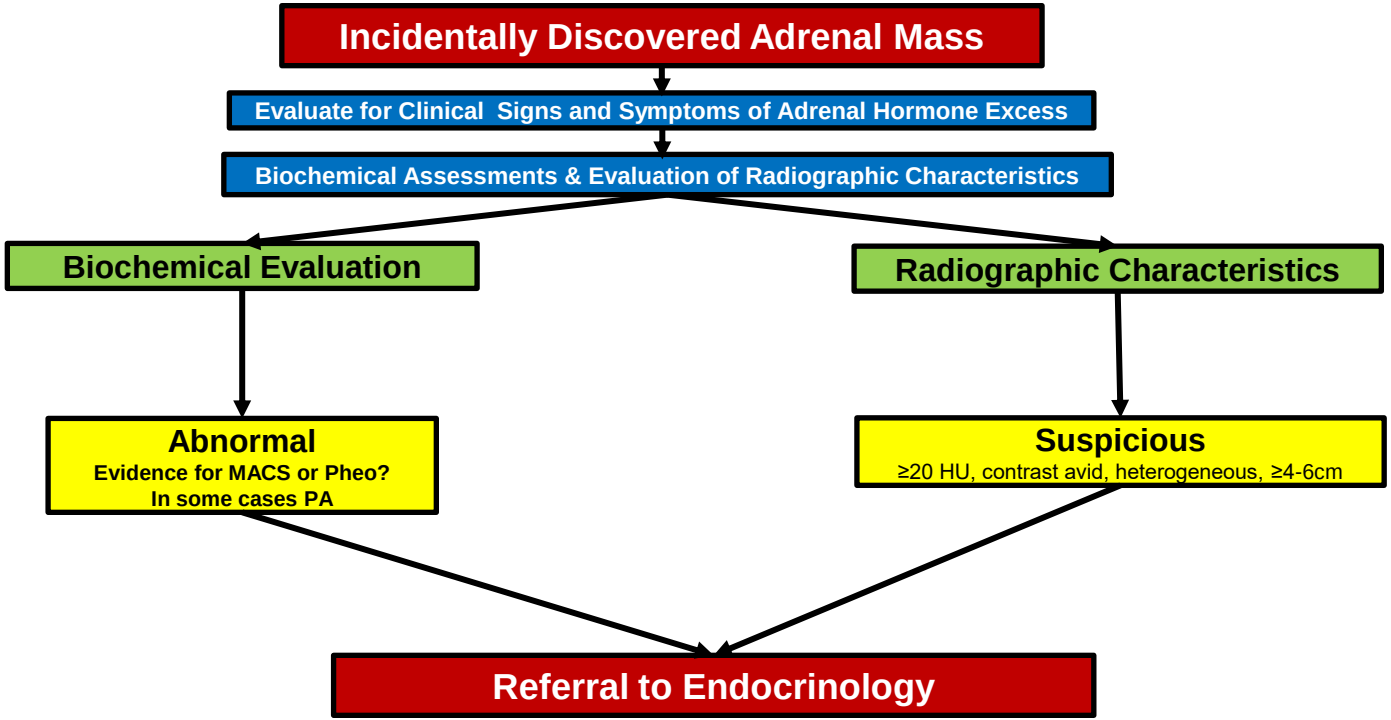
MACS is autonomous cortisol secretion without overt Cushing syndrome

Mild Autonomous Cortisol Secretion (MACS) is **<u>common</u>**

**MACS contributes to cardiometabolic disease**

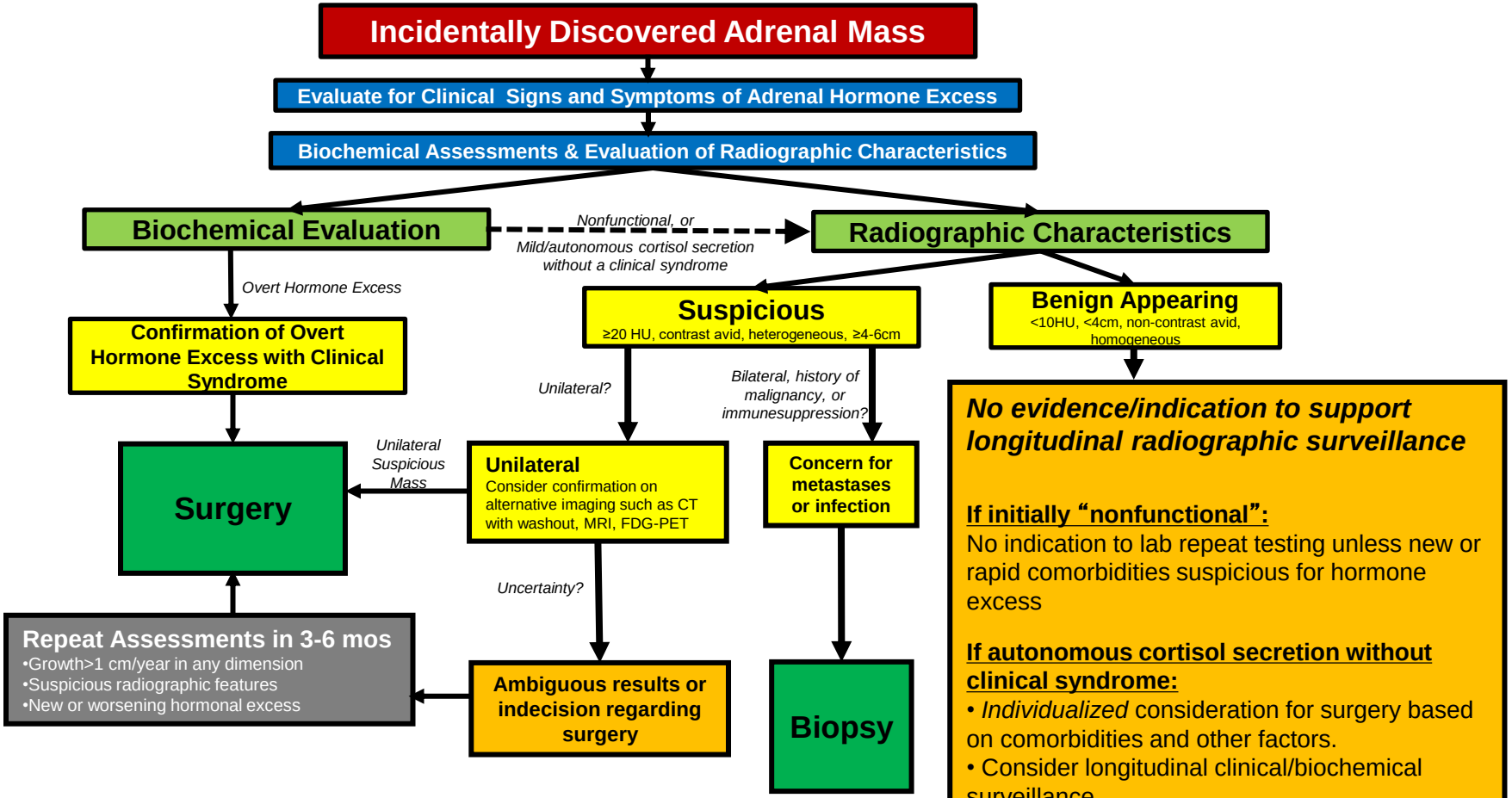
**(Anxiety/stress/pain, Anti-depressants)**

# SIMPLIFIED Approach to the Incidentally Discovered Adrenal Mass




**If a lipid-rich adenoma and no evidence of hormone excess**: no need for referral, no need for repeated imaging, no need for repeated biochemical testing, unless dramatic/unexpected changes in clinical status

# Comprehensive Approach to the Incidentally Discovered Adrenal Mass




Vaidya et al. Endocrine Practice 2019

# Summary

Primary aldosteronism is a highly prevalent, but largely unrecognized, syndrome. All patients with hypertension (but at minimum those with resistant hypertension and/or hypokalemia) should be screened at least once using a liberalized diagnostic approach

Understanding the pathophysiology of adrenal insufficiency can guide the approach to diagnosis and treatment; a morning cortisol, ACTH, DHEAS is the most pragmatic approach to diagnosis

Incidentally discovered adrenal masses are common. All adrenal masses should be evaluated for malignancy and adrenal hormone excess.

Brigham and Women's Hospital
Founding Member, Mass General Brigham

# Adrenal Disorders

**Anand Vaidya, MD MMSc**
Director, Center for Adrenal Disorders
Chief (Interim), Division of Endocrinology, Diabetes, & Hypertension
Brigham and Women's Hospital
Associate Professor of Medicine, Harvard Medical School
anandvaidya@bwh.harvard.edu