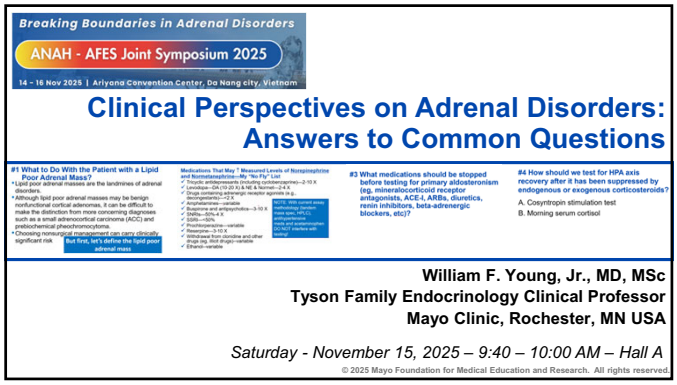


1

DISCLOSURE*

William F. Young, Jr., MD, MSc

Has consulting a relationship with:

- Crinetics Pharmaceuticals Inc. (Scientific Advisory Board)

Off Label Usage: None

*A provider must disclose the above information to learners prior to beginning of the educational activity (ACCME)

2

#1 What to Do With the Patient with a Lipid Poor Adrenal Mass?

- Lipid poor adrenal masses are the landmines of adrenal disorders.
- Although lipid poor adrenal masses may be benign nonfunctional cortical adenomas, it can be difficult to make the distinction from more concerning diagnoses such as a small adrenocortical carcinoma (ACC) and prebiochemical pheochromocytoma.
- Choosing nonsurgical management can carry clinically significant risk

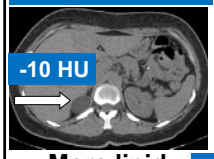
But first, let's define the lipid poor adrenal mass

3

"Imaging Phenotype"

CT attenuation measured in Hounsfield Units (HU)

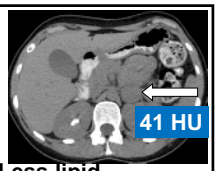
Unenhanced CT attenuation <10 HU



More lipid
Benign

+60 HU

-20 HU



Less lipid
ACC
Met
Pheo
Lipid-poor adenoma

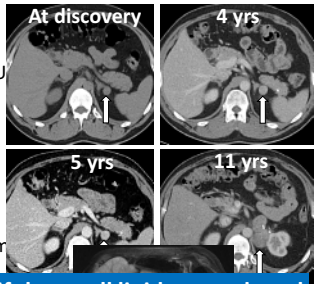
Unenhanced CT attenuation >20 HU

NOTE: Washout CT has limited utility in evaluating incidental adrenal nodules in patients without known malignancy.
Corwin MT, et al. *AJR Am J Roentgenol*. 2022;219(5):804-812.

4

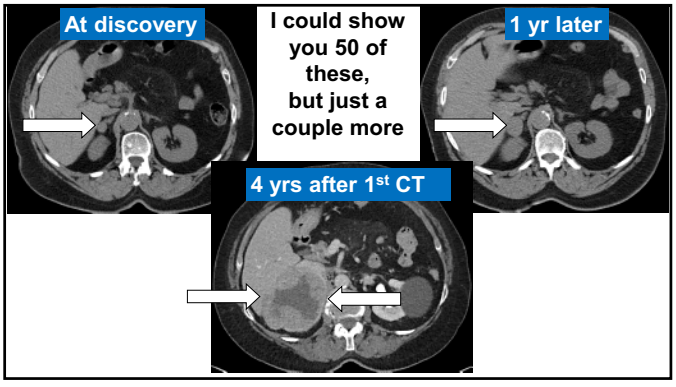
40-Yr-Old Man

- 1.6 cm LT adrenal mass with unenhanced CT attenuation = 39.1 HU
- Lab eval: normal plasma fx meta-nephrines, serum cortisol, DHEA-S
- At 9 yrs (2 yrs before coming to Mayo Clinic) he underwent left adx after the LT adrenal mass had markedly enlarged.
- The "11-yrs" image shows 3.6 x 4.4 cm recurrent ACC



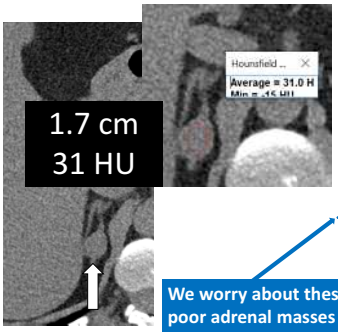
This early death was avoidable if the small lipid poor adrenal mass was resected when first detected—9 yrs before his first surgery!

5



6

50-Yr-Old Woman

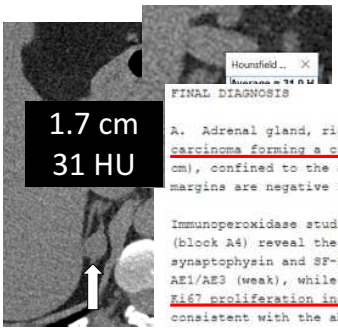


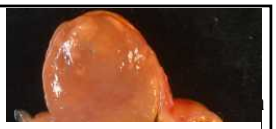
- 1.7 cm LT adrenal mass with an unenhanced CT attenuation of 31 HU
- Lab eval: normal plasma fx metanephrines, 1-mg DST, and DHEA-S
- This is most likely one of the following:
  - ✓ Pre-biochemical pheo
  - ✓ Lipid poor adenoma
  - ✓ Pre-ACC
  - ✓ ACC

We worry about these and recommend resection of lipid poor adrenal masses with an expert adrenal surgeon

7

50-Yr-Old Woman





FINAL DIAGNOSIS

A. Adrenal gland, right, adrenalectomy: Adrenal cortical carcinoma forming a circumscribed nodule (1.8 x 1.7 x 1.3 cm), confined to the adrenal gland. The surgical resection margins are negative for tumor.

Immunoperoxidase studies performed on paraffin sections (block A4) reveal the neoplastic cells are positive for synaptophysin and SF-1 and focally positive for keratin AE1/AE3 (weak), while negative for CAM 5.2 and S100. The Ki67 proliferation index is 10%. These findings are consistent with the above diagnosis.

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#1 What to Do With the Patient with a Lipid Poor Adrenal Mass?

- Lipid poor adrenal masses are the landmines of adrenal disorders.
- Although lipid poor adrenal masses may be benign nonfunctional cortical adenomas, it can be difficult to make the distinction from more concerning diagnoses such as a small adrenocortical carcinoma (ACC) and prebiochemical pheochromocytoma.
- Choosing nonsurgical management can carry clinically significant risk

But first, let's define the lipid poor adrenal mass

My Answer: After appropriate W/U, most (use common sense) lipid poor adrenal masses should be resected by an expert endocrine surgeon

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#2 You want to do biochemical testing for pheochromocytoma, but the patient is taking a potentially interfering medication. What to do?

10

Medications That May ↑ Measured Levels of Norepinephrine and Normetanephrine—My "No Fly" List

- ✓ Tricyclic antidepressants (including cyclobenzaprine)—2-10 X
- ✓ Levodopa—DA (10-20 X) & NE & Normet—2-4 X
- ✓ Drugs containing adrenergic receptor agonists (e.g., decongestants)—<2 X
- ✓ Amphetamines—variable
- ✓ Buspirone and antipsychotics—3-10 X
- ✓ SNRIs—50%-4 X
- ✓ SSRI—<50%
- ✓ Prochlorperazine—variable
- ✓ Reserpine—3-10 X
- ✓ Withdrawal from clonidine and other drugs (eg, illicit drugs)--variable
- ✓ Ethanol--variable

NOTE: With current assay methodology (tandem mass spec, HPLC), antihypertensive meds and acetaminophen DO NOT interfere with testing!

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Patient Taking a Med on the "No Fly" List—What to Do? 3 Options:

A) Go ahead & test → if labs are normal, you are golden!

B) Test and if labs abnormal, stop the drug and re-test:

- ✓e.g., if taking a TCA, stop the TCA, wait 3 to 4 wks & re-test

C) If you cannot stop the drug and if labs are abnormal and if your clinical suspicion for pheo is high, image abdomen and pelvis with CT or MRI:

- ✓85% of catechol-secreting tumors are in the adrenals
- ✓95% of catechol-secreting tumors are in the abd and pelvis
- ✓The avg size of a symptomatic catechol-secreting tumor is 4.5 cm—they are not hard to find!

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#3 What medications should be stopped before testing for primary aldosteronism (eg, mineralocorticoid receptor antagonists, ACE-I, ARBs, diuretics, renin inhibitors, beta-adrenergic blockers, etc)?

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Typical Case: 54-yr-old Man

Bill was diagnosed with hypertension more than 20 years ago. He is currently on a 7 drug program (hydralazine 100 mg 3 times per day, spironolactone 25 mg 3 times per day, carvedilol 12.5 mg twice daily, furosemide 20 mg once daily, chlorthalidone 25 mg once daily, amlodipine 10 mg once daily, and lisinopril of 40 mg daily) and his blood pressure is well controlled. His hypokalemia dates back to 2008 where I found serum potassium levels of 3.2 and 3.4 mEq per L. In 2009 potassium levels were 3.2 and 3.5

	3/11/2021 1535	
Aldosterone, P	24 *	(666 pmol/L)
OTHER ENDOCRINE		
Renin Activity, P	<0.6 *	

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Unfortunately, I see Bill's scenario every week

- Bill, with his 7-drug hypertension, had hypokalemia dating back 13 yrs. It is likely that he was never tested for PA because clinicians thought that they couldn't—due to his potentially interfering meds. Now he had stage 3 CKD.
- Although all of Bill's meds can affect the RAA system in people without PA, THEY RARELY CAUSE A PROBLEM IN PATIENTS WITH TRUE PA
- If renin is suppressed (PRA <1 ng/mL/hr or PRC <8 mU/L), then meds are not interfering and you can do any test you want—case detection testing, confirmatory testing, and AVS on ANY DRUG!!!

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*Caveat on Mineralocorticoid Receptor Antagonists

- Spironolactone (SPL) and eplerenone (EPL) do not directly affect the laboratory measurement of aldosterone
- SPL and EPL can only affect the evaluation of PA if the dosage is high enough to completely block the mineralocorticoid receptors so that the patient becomes volume depleted and renal renin secretion increases
- If renin measurements are high, the clinician cannot distinguish between PA and secondary aldosteronism
- However, if renin is suppressed (PRA <1 ng/mL/hr) while treated with MRAs, they have no impact on the evaluation of PA and you can do any test you want during treatment with with SPL or EPL

*WF Young. Diagnosis of primary aldosteronism. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed July 20, 2025.

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*Caveat on Mineralocorticoid Receptor Antagonists

- Spironolactone (SPL) and eplerenone (EPL) do not directly affect the laboratory measurement of aldosterone
- SPL and EPL can only affect the evaluation of PA if the dosage

Clinical Pearl: Most patients with PA who are treated with SPL or EPL are on subtherapeutic doses and renin will be suppressed—never stop SPL or EPL to screen for PA

*WF Young. Diagnosis of primary aldosteronism. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed November 7, 2025.

17

#3 What medications should be stopped before testing for primary aldosteronism (eg, mineralocorticoid receptor antagonists, ACE-I, ARBs, diuretics, renin inhibitors, beta-adrenergic blockers, etc)?

NONE!

This advice is based on common sense and clinical experience and this has been my recommended approach for more than 3 decades and now . . .

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Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

Gail K. Adler,[1] Michael Stowasser,[2] Ricardo R. Correa,[3] Nadia Khan,[4] Gregory Kline,[5] Michael J. McGowan,[6] Paolo Mulatero,[7] M. Hassan Murad,[8] Rhian M. Touyz,[9] Anand Vaidya,[1] Tracy A. Williams,[10] Jun Yang,[11,12] William F. Young,[8] Maria-Christina Zennaro,[13,14] and Juan P. Brito[8,15]

- Manage interfering medications depending on individual safety and feasibility. The Guideline Development Panel outlined both minimal-withdrawal and no-withdrawal strategies of interfering medications before screening (Tables 6 and 7, Fig. 1).

Adler GK, Stowasser M, Correa RR, Khan N, Kline G, McGowan MJ, Mulatero P, Murad MH, Touyz RM, Vaidya A, Williams TA, Yang J, Young WF, Zennaro MC, Brito JP. Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2025;110(9):2453-2495.

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Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

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Most important changes in the 2025 guideline:

1) All people with hypertension should be screened for PA
2) Don't have to stop meds to screen for PA
3) Only proceed with subtype testing if high probability of unilateral adrenal disease
4) More liberal use of MRAs

Adler et al. Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, 2025;, dgaf284, https://doi.org/10.1210/clinem/dgaf284

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#4 How should we test for HPA axis recovery after it has been suppressed by endogenous or exogenous corticosteroids?

A. Cosyntropin stimulation test

B. Morning serum cortisol

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ORIGINAL ARTICLE WILEY

Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess

- ✓Retrospective study of 81 patients with subclinical CS and moderate-to-severe adrenal-dependent CS who developed adrenal insufficiency after unilateral adrenalectomy (adx) (1998 – 2017)
- ✓HPA axis recovery occurred at a median of 4.3 months after adx: severe CS vs moderate CS vs SCS: median 11.4 vs 2.8 vs 2.1 months

Hurtado MD, Cortes T, Natt N, Young WF Jr, Bancos I. Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. *Clin Endocrinol* (Oxf). 2018;89:721-733.

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ORIGINAL ARTICLE WILEY

Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess

Maria Daniela Hurtado | Tiffany Cortes | Neena Natt | William F. Young Jr | Irina Bancos

- But what proved to be controversial during the peer review process was how we monitored for HPA axis recovery . . .

Hurtado MD, Cortes T, Natt N, Young WF Jr, Bancos I. Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. *Clin Endocrinol* (Oxf). 2018;89:721-733.

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Mayo Clinic Approach to Glucocorticoid Taper

- Home on prednisone 10-0-5-0 mg (if ectopic use higher dose), then drop total dosage by 2.5 mg every 2 wks:
  - ✓7.5-0-5-0 → 5-0-5-0 → 5-0-2.5-0 mg
- Then substitute hydrocortisone (HC) 20-0-10-0 mg, then drop total dose by 5 mg every 2 wks:
  - ✓15-0-10-0 → 15-0-5-0 → **15-0-0-0 mg**
- Then, no further dosage taper; but rather check 8 AM cortisol before morning dose of HC every 6 wks
- When morning serum cortisol is >10 mcg/dL (>276 nmol/L), stop HC

This same approach is used for iatrogenic CS with taper and D/C of exogenous corticosteroids

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Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess

Hurtado MD, Cortes T, Natt N, Young WF Jr, Bancos I. Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. Clin Endocrinol (Oxf). 2018;89:721-733.

Notably, the approach at our institution to the diagnosis of adrenal insufficiency (and especially recovery from adrenal insufficiency) in this unique population of patients following adrenalectomy for a cortisol-secreting adenoma does not follow the Endocrine Society guidelines.[28,29] However, it is important to note that any test should be interpreted based on the pretest probability and that the diagnostic accuracies of an 8 AM serum cortisol concentration and the cosyntropin stimulation test for primary and secondary adrenal insufficiency are not perfect.[30] The cosyntropin stimulation test simply evaluates the adrenal response to cosyntropin; the 8AM cortisol concentration assesses the entire HPA axis recovery. At the Mayo Clinic, we do not use stimulation tests to assess HPA axis recovery; but rather, once the 8 AM serum cortisol concentration is ≥10 µg/dL (≥276 nmol/L), daily GC are discontinued and patients are advised to use stress dose GC during sick days for a total of 12 months after GC are stopped.

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Patient Education is Key

MAYO CLINIC

PATIENT EDUCATION

Tapering Your Steroid Medication

You have been taking a high dose of a cortisone-like medication. Your physician has decided that you do not need to take that steroid medication long term to treat your disorder.

This information is provided to help you slowly reduce ("taper") your high-level dose of that medication. The goal of tapering is to slowly adjust your body to lower levels of cortisone. Tapering is done until you reach the "normal" range.

To help you taper, your physician may prescribe a shorter-acting, cortisone-like medication. Two examples are prednisone and hydrocortisone.

It will take many weeks or months to taper off of your steroid medication

The number of weeks it will take depends on either how long you were taking the steroid and what dosage

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Withdrawal symptoms

Everyone who tapers off of a steroid medication goes through "withdrawal." This includes having flu-like symptoms — muscle aches and nausea. Going through this stage is a common and necessary "side effect" of tapering your medication. If you feel so bad that you are curled up in bed and can't go to work or school, your care team will need to slow your tapering schedule or change your dosage.

Everyone has withdrawal symptoms. But the goal is to reduce your medication slowly enough that you can handle your symptoms and continue to do your daily activities. Call your care team if you have strong withdrawal symptoms.

Your tapering schedule for (steroid name): _____

Ask your health care provider to write on the chart below what dose you should take at each of the times noted here.

	Breakfast-time dose	Afternoon dose	Evening-meal dose	Bedtime dose
For the first _____ weeks				
For the next _____ weeks				

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Key Message:

- Simply check morning serum cortisol before the morning dose of hydrocortisone to monitor for HPA axis recovery
- When morning cortisol is >10 mcg/dL (>276 nmol/L), HPA axis has recovered
- No need for cosyntropin/synacthen (ACTH) stimulation tests!

Hurtado MD, Cortes T, Natt N, Young WF Jr, Bancos I. Extensive clinical experience: Hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. *Clin Endocrinol* (Oxf). 2018;89:721-733.

28

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Take Home Points

- **Lipid poor adrenal mass:** after appropriate W/U → consider surgery!
- **Patient on meds that could cause false + testing for pheo:** Go ahead & test → if labs are normal, you are golden!; if abnl, stop the drug and re-test; if you cannot stop the drug & labs are abnl, and if your clinical suspicion for pheo is high, image abdomen and pelvis with CT or MRI
- **Testing for PA:** don't stop meds, just test in ALL patients with ↑BP!
- **How to assess HPA axis recovery:** simply measure 8 AM serum cortisol

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Breaking Boundaries in Adrenal Disorders

ANAH - AFES Joint Symposium 2025

14 – 16 Nov 2025 | Ariyana Convention Center, Da Nang city, Vietnam

Clinical Perspectives on Adrenal Disorders: Answers to Common Questions

William F. Young, Jr., MD, MSc
Tyson Family Endocrinology Clinical Professor
Mayo Clinic, Rochester, MN USA

Saturday - November 15, 2025 – 9:40 – 10:00 AM – Hall A

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