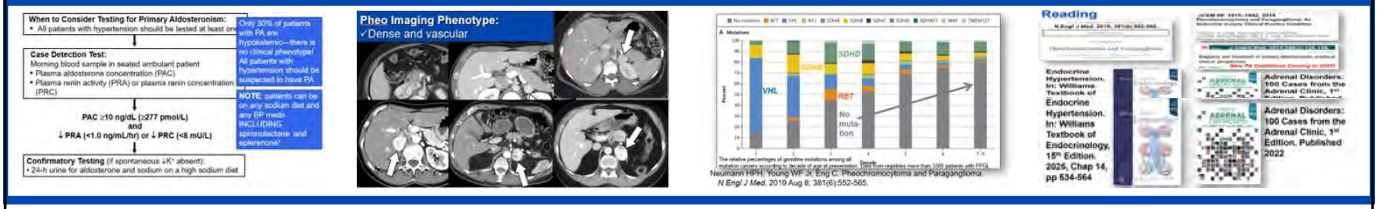
Endocrine Hypertension: Case-Based Update on Pheochromocytoma and Primary Aldosteronism



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

ANAH Online Masterclass
Saturday – November 23, 2024 – 10:10 – 11:10 AM

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

Primary Aldosteronism (PA)

- Adrenal hypersecretion of aldosterone – independent of renin:
  - ✓ hypertension
  - ✓ increased aldosterone levels
  - ✓ low renin levels
- Two most common causes:
  - ✓ Unilateral aldosterone-producing adenoma (APA) – Conn 1955
  - ✓ Bilateral idiopathic hyperaldosteronism (IHA)

3

Epidemiology of PA

- Compared to pre-1981 (when PA was considered rare), measuring morning blood levels of aldosterone and renin as a case-detection test, followed by aldosterone suppression for confirmatory testing, has resulted in much higher prevalence estimates for clinically important PA—**5% to 10%** of all people with hypertension and **20% in resistant hypertension***

*Brown JM, et al. *Ann Intern Med.* 2020;173(1):10-20.
*Loh KC, et al. *J Clin Endocrinol Metab*. 2000;85(8):2854-9.
*Mulatero P, et al. *J Clin Endo Metab*. 2004;89(3):1045-50.
*Käyser SC, et al. *J Clin Endocrinol Metab.* 2016;101:2826-35.

4

So, Why is Diagnosing PA Important?

- Patients with PA have 3- to 4-fold higher rates of myocardial infarction, stroke, coronary artery disease, atrial fibrillation, permanent loss of renal function, and poorer health-related quality of life than people with primary hypertension—all independent of blood pressure

5

So, Why is Diagnosing PA Important?

- Patients with PA have 3- to 4-fold higher rates of myocardial infarction, stroke, coronary artery disease, atrial fibrillation,

In view of the high prevalence and with so much to gain, we should probably be testing for PA early and a lot, right?

6

Screening for PA: A Sad State of Affairs . . .

- Stanford Health System:*
  - ✓ **2.1%** of 4,660 patients with resistant ↑BP were screened for PA
- University of Chicago Health System:**
  - ✓ **2.7%** of 36,941 pts with hypertension & ↓K^+ were screened for PA
- University of Minnesota:***
  - ✓ **4.2%** of 18,908 patients with resistant ↑BP were screened for PA
- Alberta, Canada:****
  - ✓ **0.7%** of 1.1 million people with hypertension were screened for PA
- Kaiser Permanente Southern California:*****
  - ✓ **1.9%** of 103,280 patients with resistant ↑BP were screened for PA

*Jaffe G, et al. Screening Rates for Primary Aldosteronism in Resistant Hypertension: A Cohort Study. *Hypertension*. 2020;75(3):650-659.

**Ruhle BC, et al. Keeping primary aldosteronism in mind: Deficiencies in screening at-risk hypertensives. *Surgery*. 2019;165(1):221-227.

***Zekarias K, Tessier KM. Screening Rate for Primary Aldosteronism Among Patients With Apparent Treatment-Resistant Hypertension: Retrospective Analysis of Current Practice. Endocr Pract. 2022;28(3):271-275.

****Liu Y-y et al. Outcomes of a specialized clinic on rates of investigations and treatment of primary aldosteronism. *JAMA Surgery*. 2021; 156:541-549.

*****Kim V, et al. Hyperaldosteronism Screening and Findings From a Large Diverse Population With Resistant Hypertension Within an Integrated Health System. Perm J. 2023 Nov 27:1-11.

7

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So, here is the deal:

- PA is common
- PA is associated with ↑ CV morbidity, CKD, and ↓ QoL—all of which can be prevented with early diagnosis and treatment
- But, clinicians rarely test for it!

*Jaffe G, et al. Screening Rates for Primary Aldosteronism in Resistant Hypertension

**Ruhle BC, et al. Keeping primary aldosteronism in mind: Deficiencies in screening a

***Zekarias K, Tessier KM. Screening Rate for Primary Aldosteronism Among Patient
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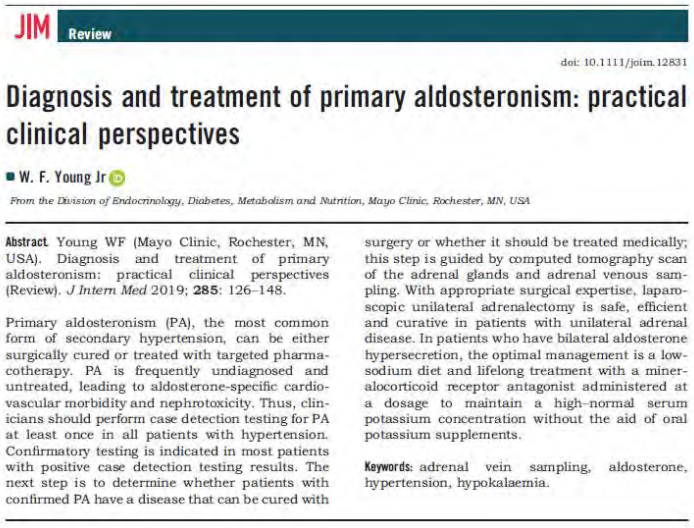
*****Kim V, et al. Hyperaldosteronism Screening and Findings From a Large Diverse Population With Resistant Hypertension Within an Integrated Health System. Perm J. 2023 Nov 27:1-11.

8

How Should We Address The Problem of Underdiagnosis of PA?

One solution:



JIM Review

doi: 10.1111/joim.12831

Diagnosis and treatment of primary aldosteronism: practical clinical perspectives

W. F. Young Jr

From the Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, MN, USA

Abstract Young WF (Mayo Clinic, Rochester, MN, USA). Diagnosis and treatment of primary aldosteronism: practical clinical perspectives (Review). *J Intern Med* 2019; **285**: 126–148.

Primary aldosteronism (PA), the most common form of secondary hypertension, can be either surgically cured or treated with targeted pharmacotherapy. PA is frequently undiagnosed and untreated, leading to aldosterone-specific cardiovascular morbidity and nephrotoxicity. Thus, clinicians should perform case detection testing for PA at least once in all patients with hypertension. Confirmatory testing is indicated in most patients with positive case detection testing results. The next step is to determine whether patients with confirmed PA have a disease that can be cured with surgery or whether it should be treated medically; this step is guided by computed tomography scan of the adrenal glands and adrenal venous sampling. With appropriate surgical expertise, laparoscopic unilateral adrenalectomy is safe, efficient and curative in patients with unilateral adrenal disease. In patients who have bilateral aldosterone hypersecretion, the optimal management is a low-sodium diet and lifelong treatment with a mineralocorticoid receptor antagonist administered at a dosage to maintain a high-normal serum potassium concentration without the aid of oral potassium supplements.

Keywords: adrenal vein sampling, aldosterone, hypertension, hypokalaemia.

Young WF Jr. Diagnosis and treatment of primary aldosteronism: practical clinical perspectives. *J Intern Med*. 2019;285(2):126-148.

9

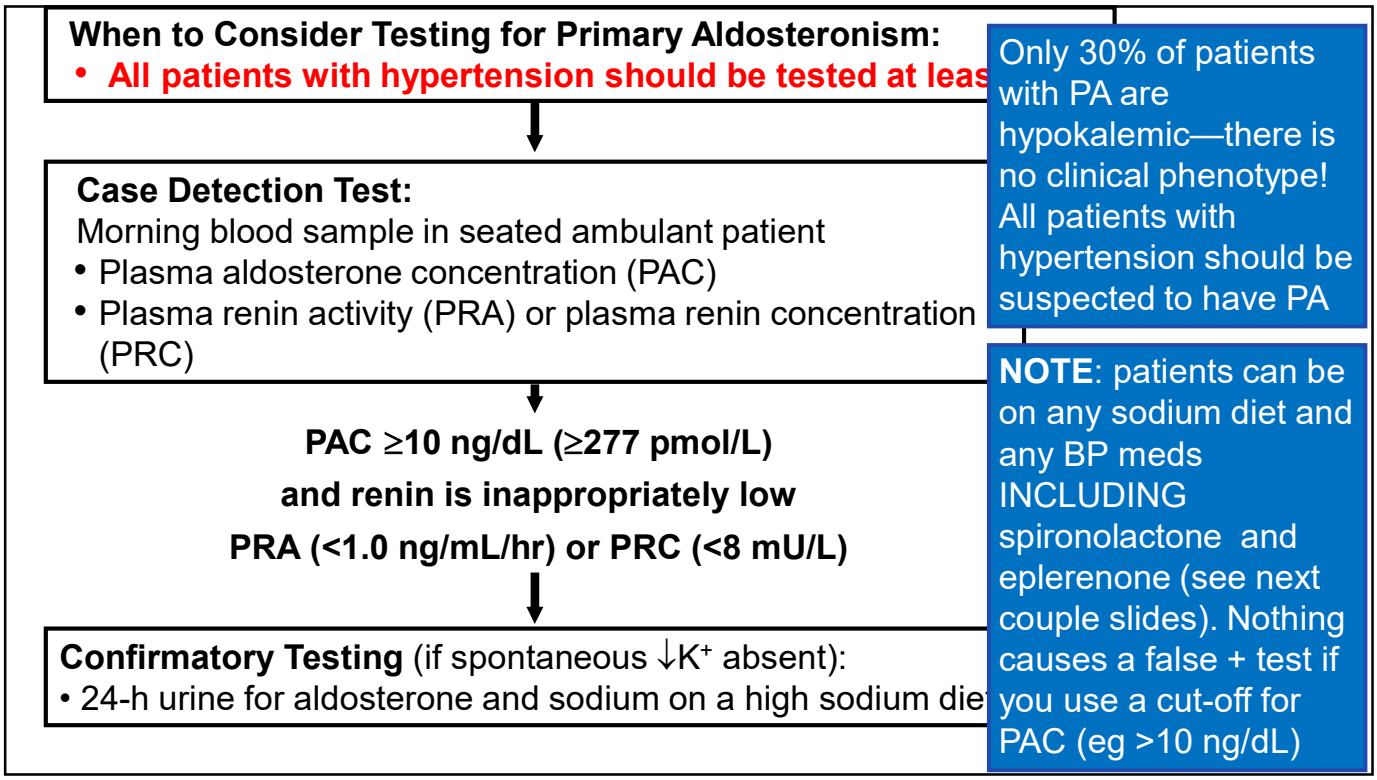
When to Consider Testing for Primary Aldosteronism:

- All patients with hypertension should be tested at least once

Over more than three decades, it has been frustrating to see patients who were not tested for PA when they were first diagnosed with hypertension, but rather only after they have developed irreversible stage 4 to 5 chronic kidney disease. Clinical practice guidelines have not been effective in driving more clinicians to consider case detection testing for PA [42]. Could the guidelines be too complicated with regard to rules on medications and by focusing on recommending subsets of patients for PA testing? The diagnostic algorithm should be simplified, and all patients with hypertension should be recommended for case detection testing for PA at least once (Fig. 1).

Young WF Jr. *J Intern Med*. 2019; 285:126-148.

10



11

63-Year-Old Woman—Came to Mayo December-2021

- Diagnosed with hypertension 11 yrs ago
- ↓K^+ first noted 8 yrs ago—aldosterone was ↑ & renin was low, CT was "negative" → Rx with spironolactone (SPL)
- 1 yr ago SPL switched to eplerenone 25 mg twice daily
- Current W/U: PAC = 40 ng/dL (1110 pmol/L) and PRA <0.6 ng/mL/hr ← **Despite eplerenone**

12

*Caveat on SPL and EPL

Mineralocorticoid receptor antagonists – Data obtained from patients treated with a mineralocorticoid receptor antagonist (spironolactone **and** eplerenone) may be difficult to interpret. These drugs prevent aldosterone from activating its receptor, resulting sequentially in sodium loss, a decrease in plasma volume, and an elevation in PRA, which could potentially lead to false-negative testing in a patient with primary aldosteronism. For this reason, spironolactone and eplerenone should not be initiated until the evaluation is completed and the final decisions about treatment are made.

However, there are exceptions to this rule. For example, if the patient has hypokalemia despite treatment with spironolactone or eplerenone, then the mineralocorticoid receptors are not fully blocked, and PRA or PRC should remain suppressed in patients with primary aldosteronism. Most patients with primary aldosteronism who are treated with mineralocorticoid receptor antagonists are given subtherapeutic doses. Thus, when there is clinical suspicion for primary aldosteronism in patients treated with spironolactone or eplerenone, PAC and PRA should be measured; if the PRA is suppressed in this setting, these medications are not interfering with the evaluation, and case-detection testing, confirmatory testing, and adrenal vein sampling (AVS) can be performed without discontinuing the mineralocorticoid receptor antagonists. However, if PRA is not suppressed, then the mineralocorticoid receptor antagonist should be discontinued for four to six weeks before retesting. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing unless the patient is on high doses.

ACE inhibitors, ARBs, direct renin inhibitors – Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and direct renin inhibitors could potentially elevate PRC and have variable effects on PRA in patients with primary aldosteronism. Thus, in a patient treated with one of these drugs, a PRA >1 ng/mL/hour does **not** exclude the diagnosis of primary aldosteronism. On the other hand, a PRA <1 ng/mL/hour or a PRC below the lower limit of normal in a patient taking one of these drugs is a strong predictor for primary aldosteronism.

*WF Young. Diagnosis of primary aldosteronism. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed January 28, 2024.

13

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So, this is simply understanding physiology. If renin is suppressed in a patient taking SPL or EPL (or any medication), you can do case detection testing, confirmatory testing, and even AVS!

*WF Young. Diagnosis of primary aldosteronism. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed November 22, 2024.

14

An Example of the Consequence Thinking That Medications are Problematic: 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 * ng/dL (666 pmol/L)
OTHER ENDOCRINE	
Renin Activity, P	<0.6 *

15

63-Year-Old Woman—Came to Mayo December-2021

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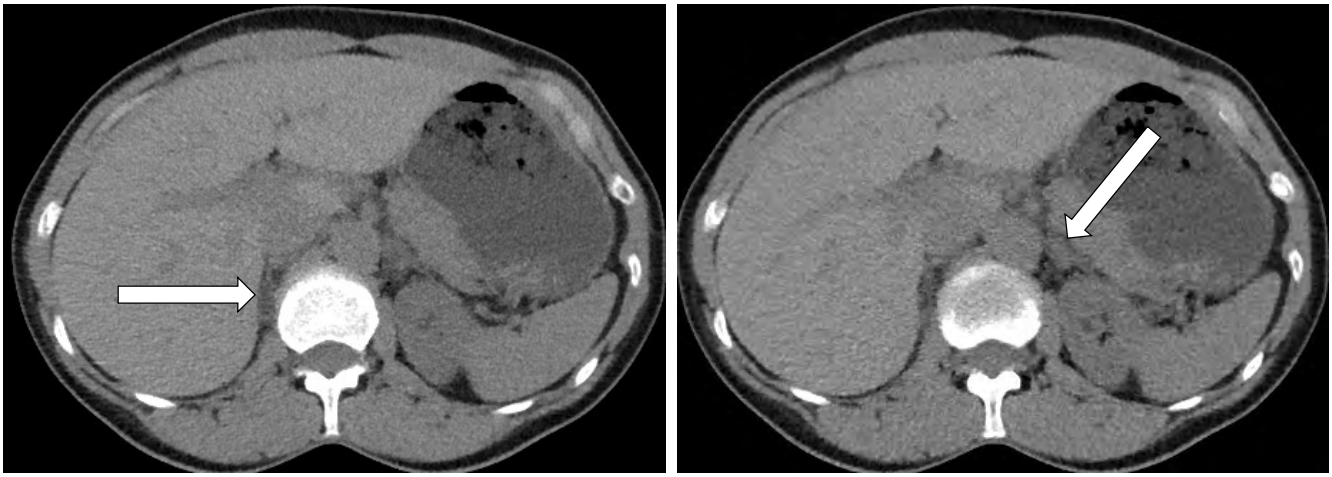
- 1 yr ago SPL switched to eplerenone 25 mg twice daily
- Current W/U: PAC = 40 ng/dL (1110 pmol/L) and PRA <0.6 ng/mL/hr ← **Despite eplerenone**
- Follows a very strict low-sodium diet
- Current CT shows an 8-mm low-density nodule in the RT adrenal gland & a very thickened LT adrenal gland

16

63-Year-Old Woman—Came to Mayo December-2021



- She seeks a surgical cure for PA

17

Adrenal Venous Sampling (with cosyntropin 50 mcg/hr)

11m ago / All Rows / Time Mark	2021 12/16/21 09:03	12/16/21 09:02	12/16/21 08:58	
ADRENAL VEIN SAM...				
Aldosterone, IVC	65			1803 pmol/L
Aldosterone, LAV		252		6990 pmol/L
Aldosterone, RAV			10300	285722 pmol/L
Cortisol, IVC	25			690 nmol/L
Cortisol, LAV		557		15367 nmol/L
Cortisol, RAV			879	24250 nmol/L

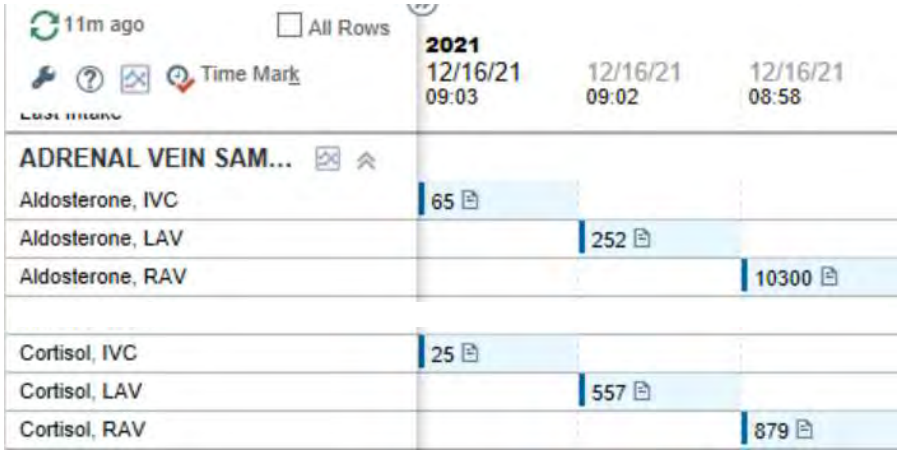
To convert to SI units:

Aldosterone ng/dL x 27.74 for pmol/L

Cortisol mcg/dL x 27.588 for nmol/L

18

Adrenal Venous Sampling (with cosyntropin 50 mcg/hr)



Q #1: Was AVS bilaterally successful?

Both AV cortisols must be 5-fold greater than IVC

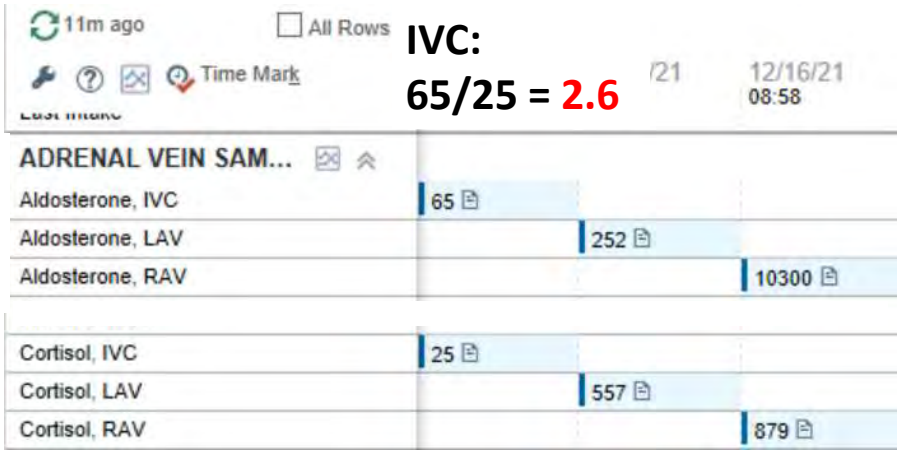
RT AV: 879/25 = 35.2-fold

LT AV: 557/25 = 22.3-fold

19

Adrenal Venous Sampling (with cosyntropin 50 mcg/hr)

RT AV: 10300/879 = 11.7



IVC: 65/25 = 2.6

LT AV: 252/557 = 0.5

Q #2: Does the patient have unilateral or bilateral disease?

a) Divide [aldo] by respective [cortisol]

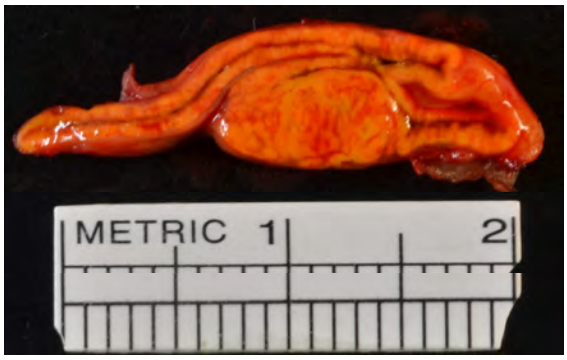
b) Divide dominant adrenal A/C ratio by non-dominant adrenal

11.7 / **0.5** = **23.4-to-1** (**RIGHT**-to-left) (> 4-to-1 = unilateral)

20

Outpatient Lap RT Adx Jan-12-2022: 45 min surgery:

0.8 x 0.6 x 0.5 cm, yellow, soft mass located in the cortex



Time Mark	1/13/22 08:00
Aldosterone, P	<4.0

21

5-month postop follow-up

Young, William Jr., M.D.
Physician
END (Endocrinology)

Progress Notes

Encounter Date: 6/4/2022

6/4/2022

#1 Primary Aldosteronism: RIGHT Adrenal Gland Disease--S/P Right Adrenalectomy January 13, 2022

Debbie recently communicated with me by e-mail and wrote:
"I think of you (and of Mayo) so often, as I'm doing really well and feeling so grateful for no longer being a PA patient. I had bloodwork done in late April, through my local doctor. My results were very good: aldosterone 2 ng/dL, renin 1.41 ng/mL/hr, ARR 1.4, and potassium, sodium, and creatinine were all normal. My blood pressure has been amazing! It averages 110/65 mmHg. I'm still feeling the need to eat a higher sodium diet, as at times my blood pressure will drop a little (systolic in the low 100 range). And I forgot to mention... no BP meds!"

22

1-year postop follow-up:

Young, William Jr., M.D.
Physician
END (Endocrinology)

Progress Notes
Signed

Encounter Date: 1/2/2023

1/2/2023 - **Patient not seen - e-mail communication**

#1 Primary Aldosteronism: RIGHT Adrenal Gland Disease--S/P Right Adrenalectomy January 13, 2022

Debbie recently communicated with me by e-mail and wrote:
"It's hard to believe that a year has already gone by. I'm doing well. My blood pressure has been perfect ever since my surgery (my reading last night was 111/69). I can eat the saltiest food and my blood pressure doesn't budge, it's generally around 105-110/65-70. At my local doctor appointments, my previous "white coat syndrome" readings are a thing of the past. I am so grateful to you and the Mayo team! My most recent labs, done about two weeks ago, showed sodium at 136, potassium at 4.4, and creatinine at .9. Those results have been pretty consistent over the past year (although creatinine tends to range between .8 and .9)."

23

Treatment of Primary Aldosteronism

IHA

If severe PA and markedly asymmetric on AVS, consider unilateral surgical debulking*

Coming soon: Aldo Synthase Inhibitor**

APA and PAH

Mineralocorticoid-Receptor Antagonist

Selective: Eplerenone

Nonselective: Spironolactone

Laparoscopic Adrenalectomy

If needed for BP control, add diuretic, CCB, and/or ACE-I/ARB

Correct dose of SPL (once daily) or EPL (twice daily) is what ever it takes for a high-normal serum K^+ (eg, 4.5 mEq/L) & PRA >1 ng/mL/hr without the aid of KCl supplements

*Szabo Yamashita T, et al. Unilateral Adrenalectomy for Primary Aldosteronism Due to Bilateral Adrenal Disease Can Result in Resolution of Hypokalemia and Amelioration of Hypertension. *World J Surg*. 2023;47(2):314-318.

**Freeman MW, et al. Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension. *N Engl J Med*. 2022 Nov 7. doi: 10.1056/NEJMoa2213169. Epub ahead of print. PMID: &36342143.

24

Pheochromocytoma—Background

- ✓ Catecholamine-secreting tumor is usually localized to the adrenal gland
- ✓ **Frequently sought** and **rarely found**
- ✓ When correctly diagnosed and properly treated, it is **curable**
- ✓ When undiagnosed or improperly treated, it can be **fatal**

25

Pheo: Clinical Presentation

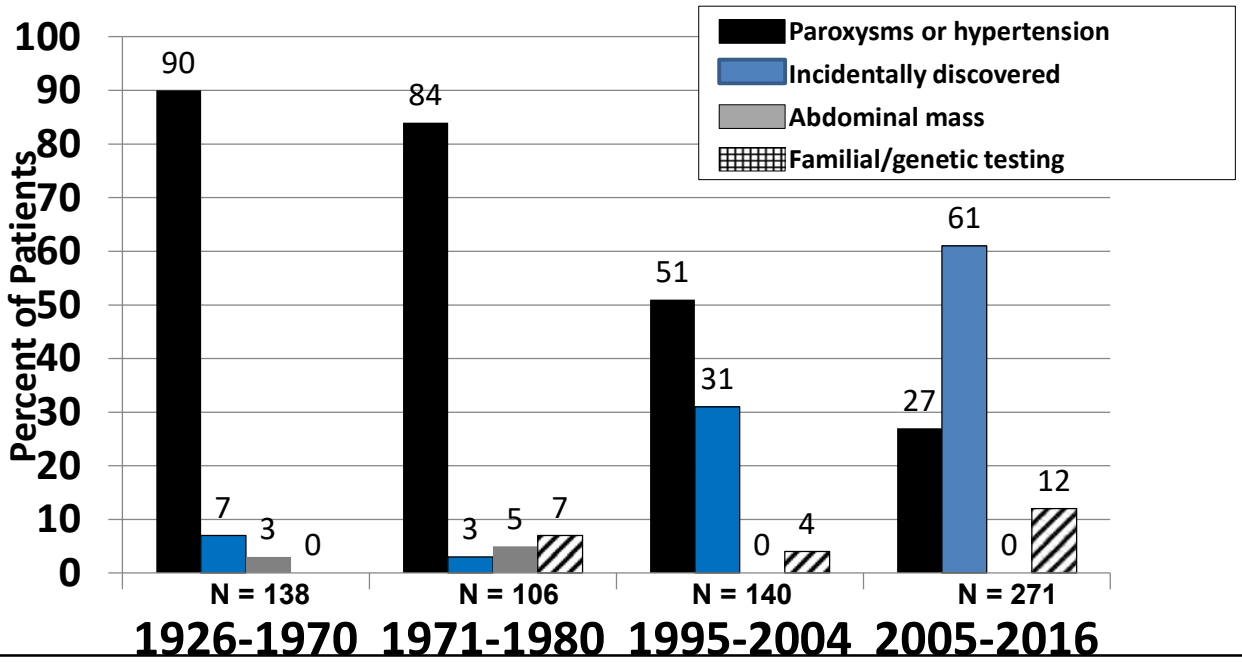
- ✓ **Prevalence** -- 0.01% to 0.1%
- ✓ **Occurrence** -- equally in men and women, primarily in the 3rd through 5th decades
- ✓ **Symptoms** – in 2024 symptoms are present <50% of patients; when present, typically paroxysmal
- ✓ **Mode of Diagnosis** – has changed dramatically over the past 100 yrs—60% are discovered as adrenal incidentalomas*

*Gruber LM, et al. Pheochromocytoma Characteristics and Behavior Differ Depending on Method of Discovery. *J Clin Endocrinol Metab*. 2019; 104(5):1386-1393.

26

Mode of Diagnosis of Pheochromocytoma at Mayo Clinic*

*Gruber LM, et al. *JCEM* 2019 ;104:1386-1393.



27

Pheo: When to Suspect:

- ✓ Hyperadrenergic spells (eg, episodes of forceful palpitations, diaphoresis, headache, tremor, **pallor**)
  HOWEVER, most patients with spells do NOT have pheo!
- ✓ Resistant hypertension
- ✓ A familial syndrome that predisposes to pheo/PGL (eg, MEN 2, NF-1, VHL, SDHx)
- ✓ A family history of pheochromocytoma
- ✓ **An incidentally discovered adrenal mass (61% of our pheo patients at Mayo Clinic!)**
- ✓ Pressor response to anesthesia, surgery, angiography, high-dose corticosteroid (eg, 8-mg overnight DST), β-blocker, metoclopramide
- ✓ Onset of hypertension at a young age (eg, <30 yrs)

NOTE: ≈2% of all adrenal incidentaloma patients have pheo

Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. *N Engl J Med*. 2019: 8;381:552-565.

28

Pheo: Case Detection

- ✓ Optimal that patients not receive any meds during lab testing; but, Rx with most meds may be continued (**all BP-related meds are OK!!!**)
- ✓ Tricyclic antidepressants (TCAs) interfere most frequently with the interpretation of 24-hr urinary fx cats & mets (**TIP: cyclobenzaprine [Flexeril®] is a TCA**)
- ✓ Rx with TCAs & antipsychotic agents should be tapered & D/C at least 4 wks before testing—frequently this is not possible → go ahead and test & if labs normal, you are done!
- ✓ Finally, catechol secretion may be appropriately ↑ed in situations of physical stress or illness (eg, stroke, MI, etc.)*

*Kline GA, et al. Inpatient Measurements of Urine Metanephrines are Indistinguishable from Pheochromocytoma: Retrospective Cohort Study. *Am J Med*. 2021;134(8):1039-1046.e3.

29

Medications That May ↑ Measured Levels of Norepinephrine and Normetanephrine

- ✓ 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
- ✓ Serotonin and norepinephrine reuptake inhibitor—50%-4 X
- ✓ Selective serotonin reuptake inhibitor—<50%
- ✓ Prochlorperazine—variable
- ✓ Reserpine—3-10 X
- ✓ Withdrawal from clonidine and other drugs (eg, illicit drugs)--variable
- ✓ Ethanol--variable

30

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- ✓ Serotonin and norepinephrine reuptake
- ✓ Selective serotonin reuptake inhibitor—
- ✓ 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 spectroscopy, HPLC), antihypertensive meds and acetaminophen DO NOT interfere with testing!

31

However, 60% of pheochromocytoma patients in 2024 are detected as adrenal incidentalomas!

When small (<1.5 cm), pheochromocytomas are not large enough to make enough catechols to be biochemically detectable AND some pheos are nonfunctional

So, it is key for endocrinologists to know what pheos "look like" – the "imaging phenotype"

32

Pheo Imaging Phenotype:
✓Dense (unenhanced CT attenuation ≥10 HU)

Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med.* 2007 Feb 8;356(6):601-10. Review. PubMed PMID: 17287480.

33

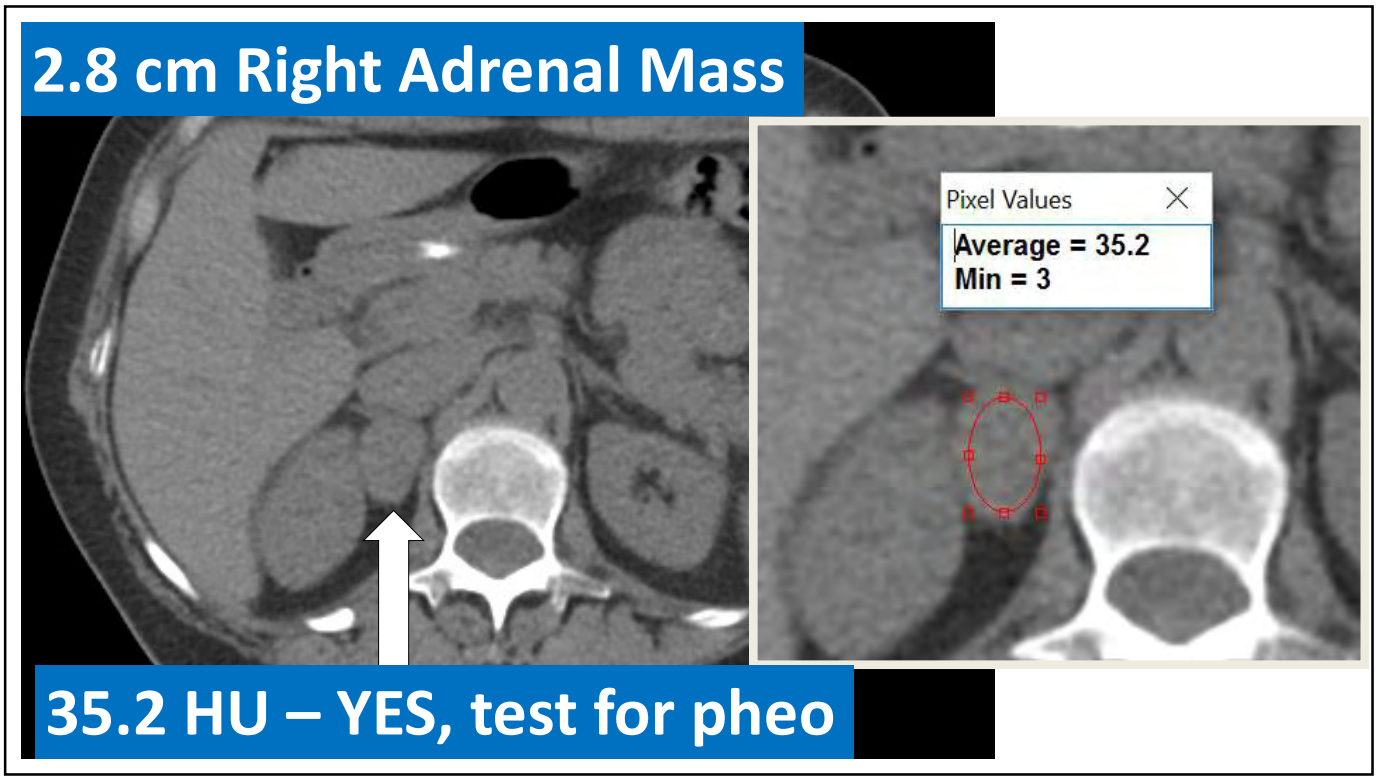
CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma

Letizia Canu,[1,2] Janna A. W. Van Hemert,[1] Michiel N. Kerstens,[3] Robert P. Hartman,[4] Aakanksha Khanna,[5] Ivana Kraljevic,[6] Darko Kastelan,[6] Corin Badiu,[7] Urszula Ambroziak,[8] Antoine Tabarin,[9] Magalie Haissaguerre,[9] Edward Buitenwerf,[3] Anneke Visser,[10] Massimo Mannelli,[2] Wiebke Arlt,[11] Vasileios Chortis,[11] Isabelle Bourdeau,[12] Nadia Gagnon,[12] Marie Buchy,[13] Francoise Borson-Chazot,[13] Timo Deutschbein,[14] Martin Fassnacht,[14,15] Alicja Hubalewska-Dydejczyk,[16] Marcin Motyka,[16] Ewelina Rzepka,[16] Ruth T. Casey,[17] Benjamin G. Challis,[17] Marcus Quinkler,[18] Laurent Vroonen,[19] Ariadni Spyroglou,[20,21] Felix Beuschlein,[20,21] Cristina Lamas,[22] William F. Young,[5] Irina Bancos,[5] and Henri J. L. M. Timmers[1]

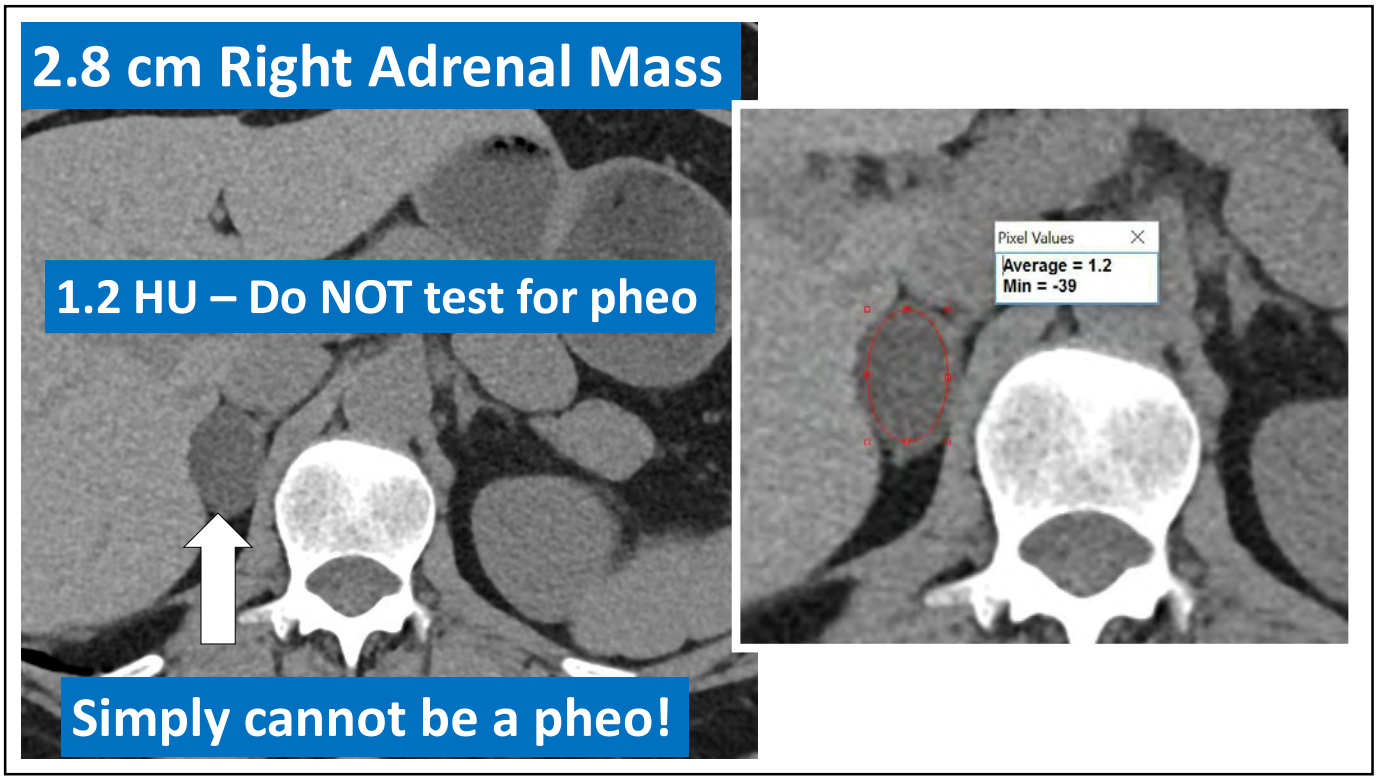
- Multicenter retrospective study of 533 patients with 548 histologically confirmed pheos
- Among the 376 pheos for which **unenhanced** CT attenuation data were available, 374 had an attenuation of >10 HU (99.5%)
- In the 2 exceptions (0.5%), the unenhanced CT attenuation was exactly 10 HU

Canu L, et al. CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma. *J Clin Endocrinol Metab*. 2019;104(2):312-18

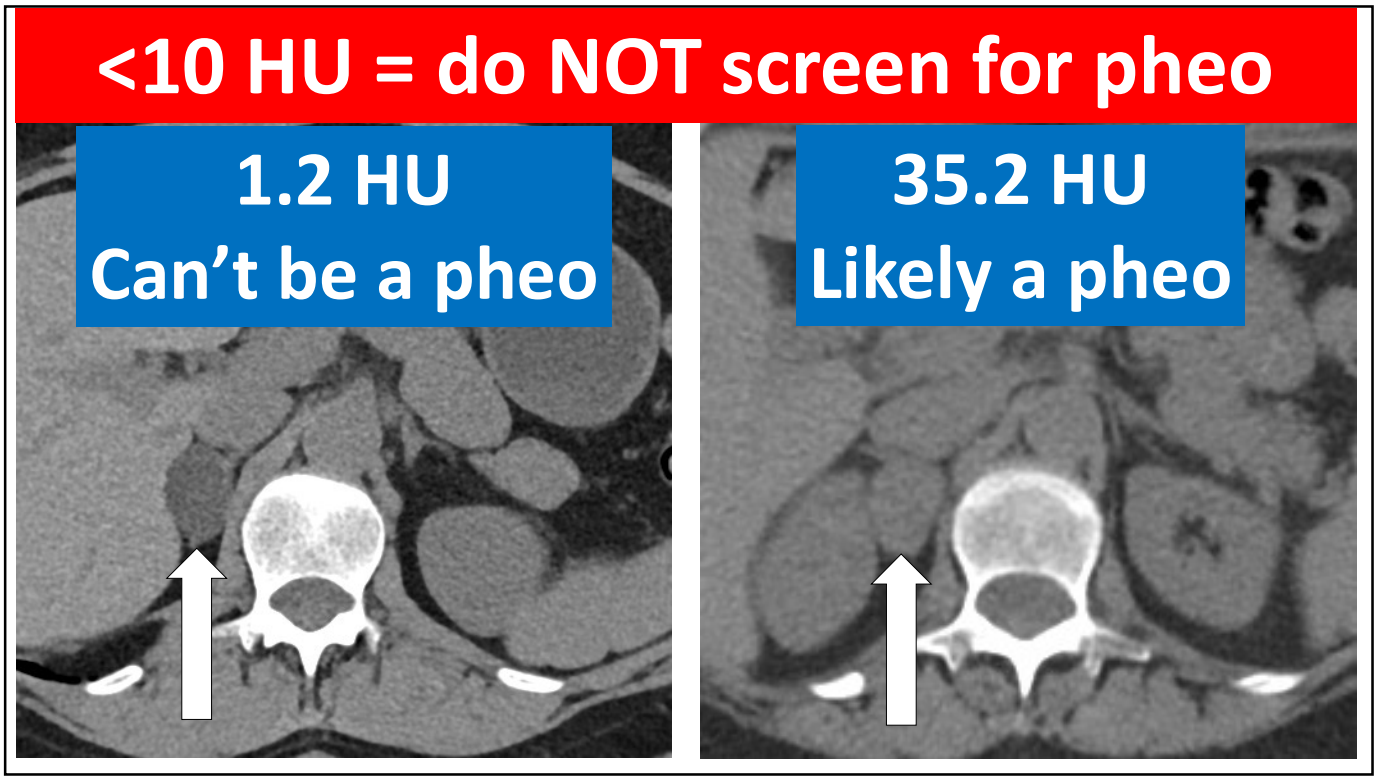
34


2.8 cm Right Adrenal Mass
Pixel Values
Average = 35.2
Min = 3
35.2 HU – YES, test for pheo

35


2.8 cm Right Adrenal Mass
1.2 HU – Do NOT test for pheo
Pixel Values
Average = 1.2
Min = -39
Simply cannot be a pheo!

36



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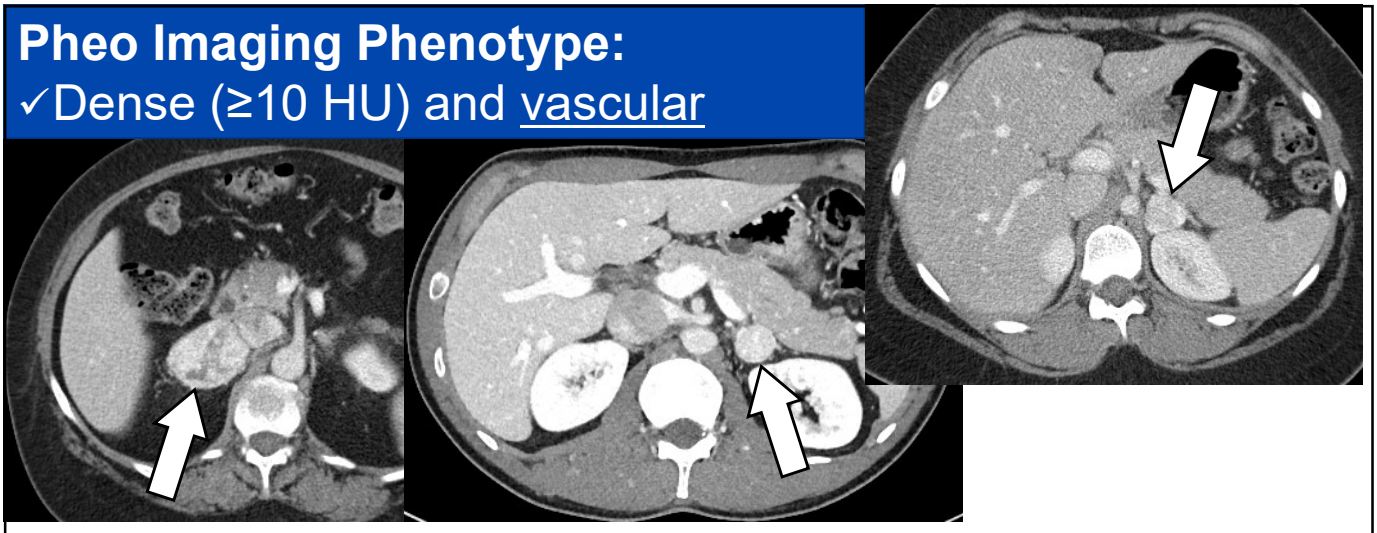
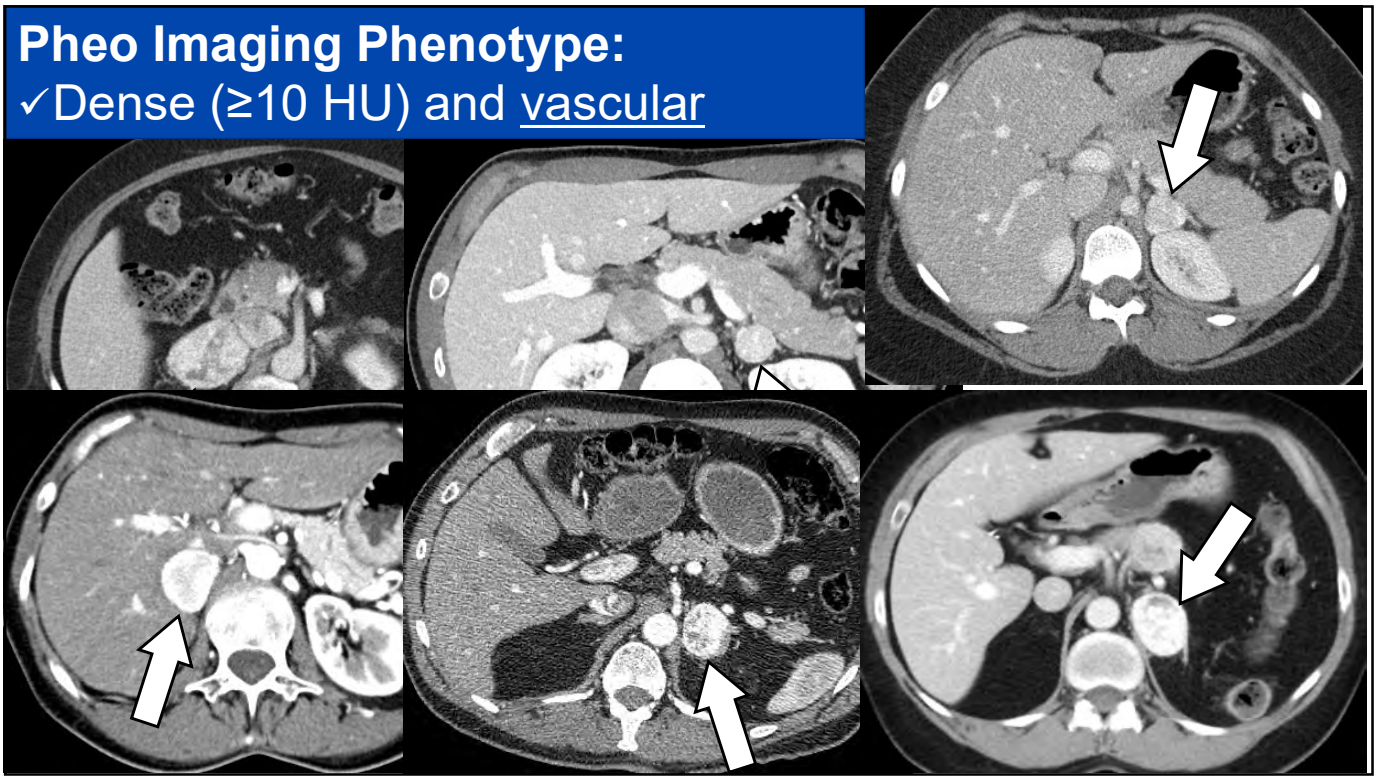


Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med.* 2007 Feb 8;356(6):601-10. Review. PubMed PMID: 17287480.

38

Pheo Imaging Phenotype:

✓Dense (≥10 HU) and vascular

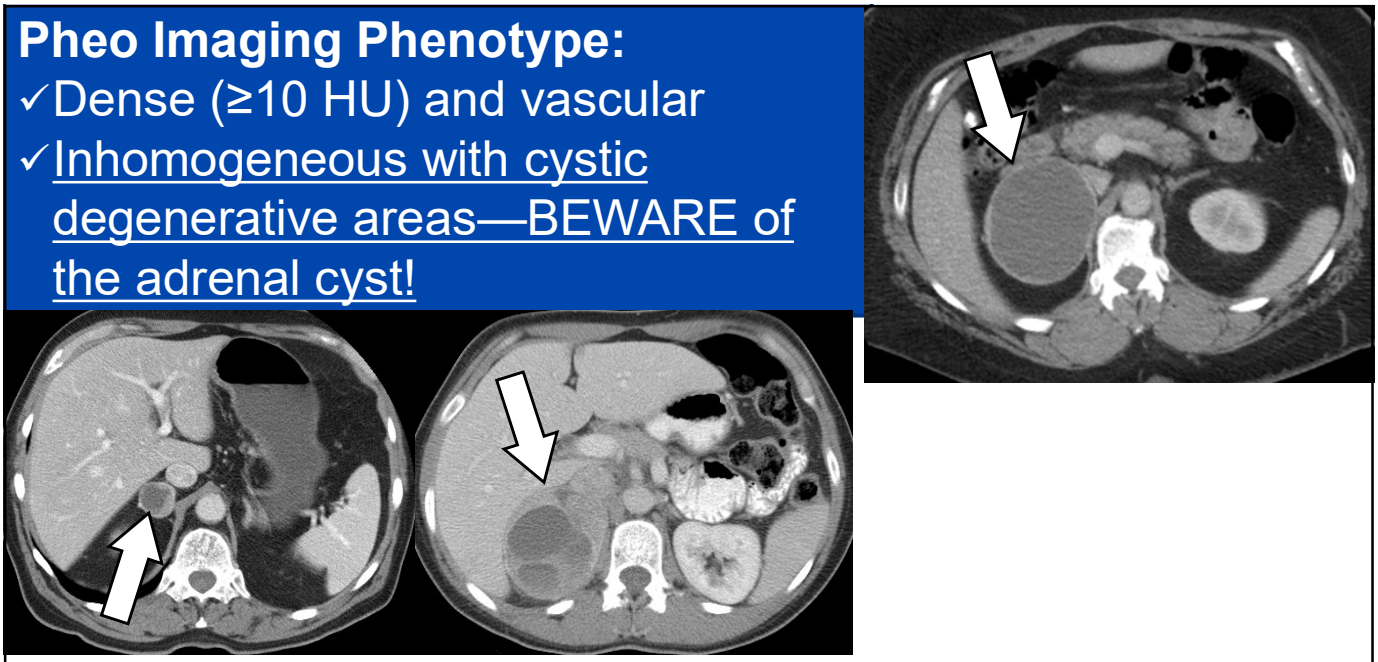


39

Pheo Imaging Phenotype:

✓Dense (≥10 HU) and vascular

✓Inhomogeneous with cystic degenerative areas—BEWARE of the adrenal cyst!

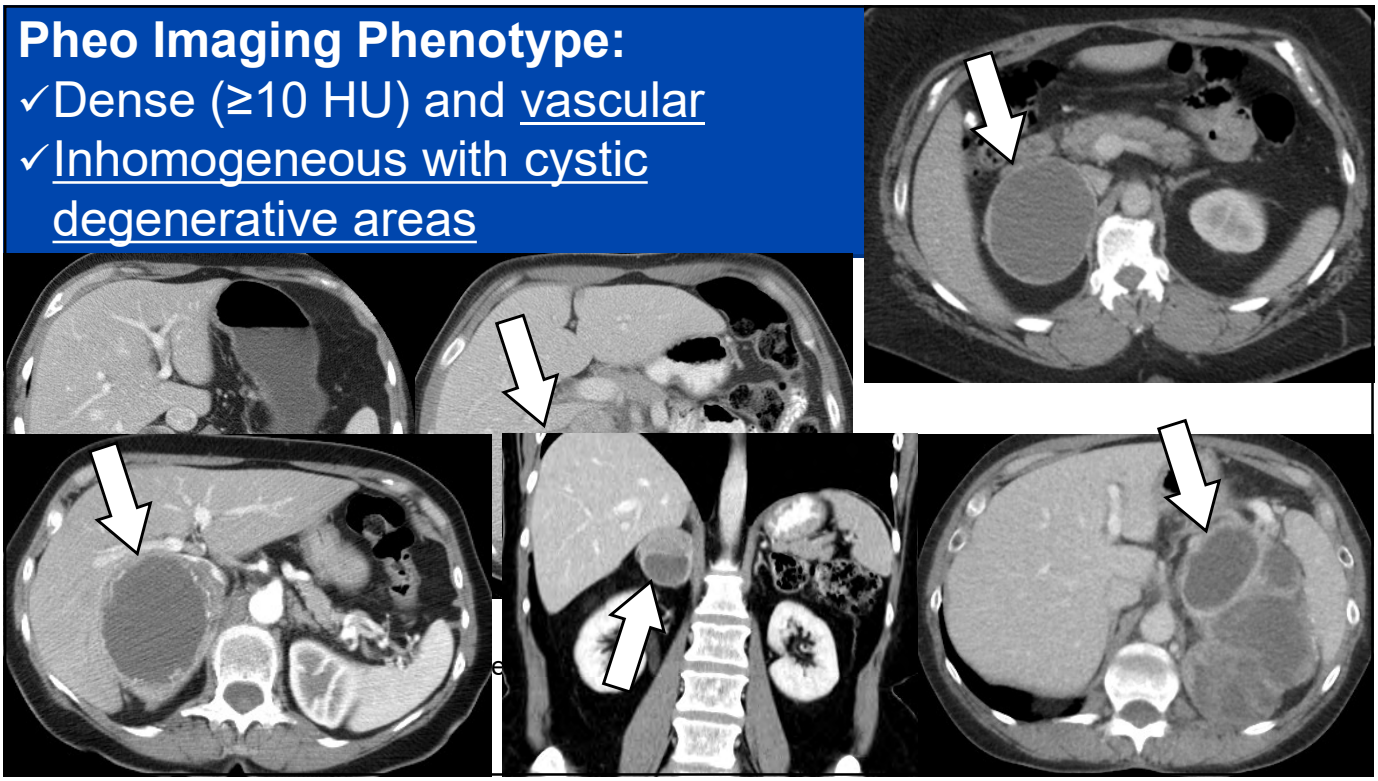


Dogra P, Navin PJ, McKenzie TJ, Foster T, Dy B, Lyden M, Young WF Jr, Bancos I. Clinical, imaging and biochemical presentation of cystic pheochromocytomas. Clin Endocrinol (Oxf). 2023 Jan;98(1):32-40.

40

Pheo Imaging Phenotype:

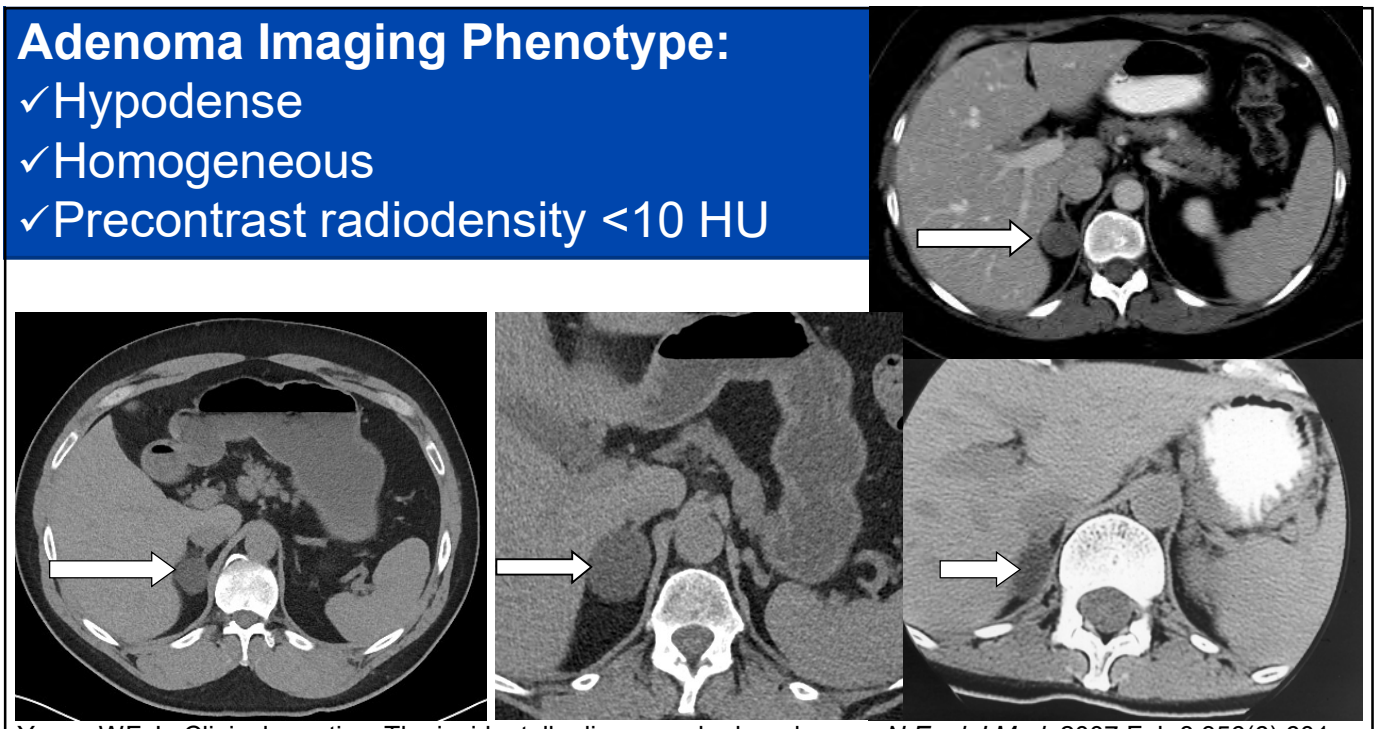
- ✓Dense (≥10 HU) and vascular
- ✓Inhomogeneous with cystic degenerative areas



41

Adenoma Imaging Phenotype:

- ✓Hypodense
- ✓Homogeneous
- ✓Precontrast radiodensity <10 HU



Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med*. 2007 Feb 8;356(6):601-10. Review. PubMed PMID: 17287480

42

The Messages Here are Simple:

- In the patient with an adrenal incidentaloma—the very first thing you should do (even before talking to the patient!) is to look at the imaging phenotype—this information directs 90% of what I will do.
- Small pheos can be "pre-biochemical"—rely on imaging phenotype

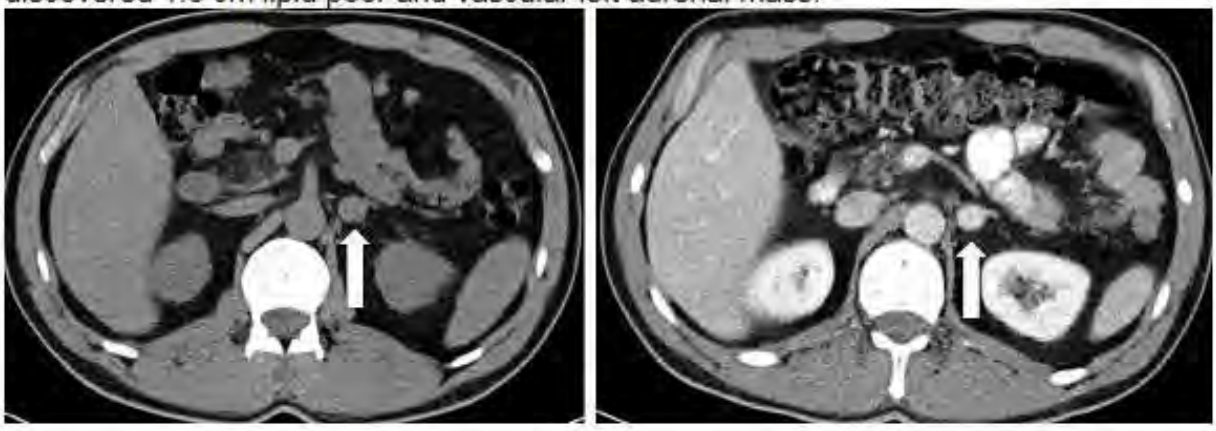
43

Chief Complaint: [redacted] is a 49-year-old [redacted] from [redacted] seen in consultation today at the request of his [redacted] for the evaluation of an incidentally discovered lipid poor and vascular 1.6 cm left adrenal mass.

History of Present Illness:

#1 Mass Adrenal (HCC)

Patient has been troubled by intermittent right upper quadrant pain, which is thought to be related to gallbladder dysfunction. In the process of imaging he had an incidentally discovered 1.6 cm lipid poor and vascular left adrenal mass.



44

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consultation today at the request of his [redacted]
of an incidentally discovered lipid poor and vascular 1.6 cm le

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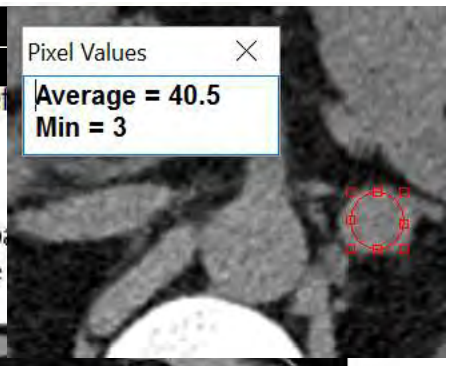
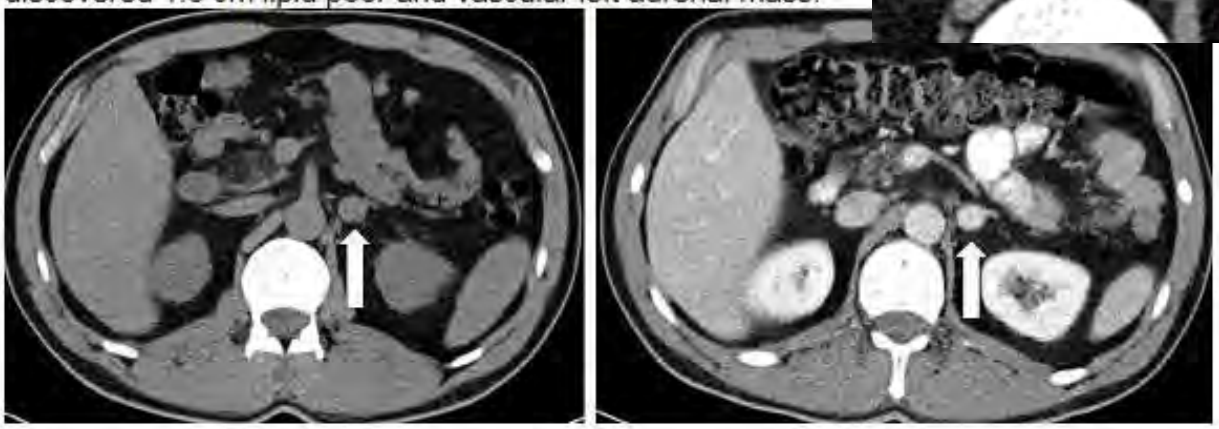




45

	Ref. Range and Units	19 3/26/2019 0709
Metanephrine, Free	Latest Range: <0.50 nmol/L	<0.20 *
Normetanephrine, Free	Latest Range: <0.90 nmol/L	0.55

	Ref. Range and Units	13 3/27/2019 0720	14 3/27/2019 0706	15 3/27/2019 0705	16 3/27/2019 0618	17 3/27/2019 0600
Dopamine	Latest Range: 65 - 400 mcg/24 h	201 *				
Epinephrine	Latest Range: <21 mcg/24 h	7.6				
Metanephrine, U	Latest Units: mcg/24 h <400 mcg					151 *
Norepinephrine	Latest Range: 15 - 80 mcg/24 h	61				
Normetanephrine, U	Latest Units: mcg/24 h <900 mcg					447 *
Sodium, U	Latest Range: 41 - 227 mmol/24 h					231
Collection Duration	Latest Units: h					24
Urine Volume	Latest Units: mL					1862
Sodium Concentration	Latest Units: mmol/L					124
Total Metanephrine...	Latest Units: mcg/24 h <1300 mcg					598 *

46

Op Note by [redacted] 3/29/2019 3:[redacted] PM

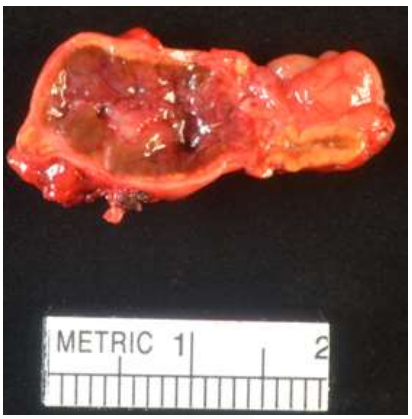
Author: [redacted]
Filed: 3/29/2019 4:43 PM
Editor: [redacted]

Service: GNS General Surgery
Date of Service: 3/29/2019 3:33 PM

FULL OP NOTE

Procedure(s) (LRB):
LAPAROSCOPIC ADRENALECTOMY, ANTERIOR. (Left)

Surgeon(s) and Role:
[redacted]



Anesthesia Type:
General

Pre-Operative Diag
Pheochromocytom

FINAL DIAGNOSIS
A. Adrenal gland, left, adrenalectomy: Pheochromocytoma, forming a 2.1 x 1.7 x 1.3 cm mass.
This final pathology report is based on the gross/macroscopic examination, the frozen section histologic evaluation of the specimen(s), and review of the Hematoxylin and Eosin (H&E) permanent sections. Any revised information from the preliminary report is underlined.

47

Message: All pheochromocytomas are "pre-biochemical" when small. Lipid poor and vascular adrenal masses should be considered as pheo or small ACC or "pre-ACC". They should either be resected (assuming you have an expert adrenal surgeon) or followed closely!

Anesthesia Type:
General

Pre-Operative Diag
Pheochromocytom

FINAL DIAGNOSIS
A. Adrenal gland, left, adrenalectomy: Pheochromocytoma, forming a 2.1 x 1.7 x 1.3 cm mass.
This final pathology report is based on the gross/macroscopic examination, the frozen section histologic evaluation of the specimen(s), and review of the Hematoxylin and Eosin (H&E) permanent sections. Any revised information from the preliminary report is underlined.

48

Common Sense Tips on Diagnosis

Additional tips:

- Fractionated plasma **normetanephrine** has a 15% false positive rate—combine that piece of information with the rarity of pheochromocytoma and you will find that 97% of patients with increased plasma **normetanephrine** will **NOT** have a pheochromocytoma!*
- However, when plasma **metanephrine** is even mildly elevated take it seriously!

*Sawka AM, et al. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab*. 2003;88:553-8.

49

Common Sense Tips on Diagnosis

- ✓ Suppression testing with clonidine or provocative testing with glucagon, histamine, or metoclopramide are NEVER needed
- ✓ In a pt with **spells**, the degree of ↑ of fx mets & cats should be markedly abnormal—in other words, if a pheo is responsible for "classic pheochromocytoma spells", then the biochemical tests are **ALWAYS** unequivocally abnormal (eg, >5-fold above the ULN)

50

Genetic Causes

Hypoxic Signaling Pathway – "Cluster 1" (Noradrenergic + DA):

- ***SDHx: SDHA, SDHAF2, SDHB, SDHC, SDHD***
- ***VHL***
- *FH*
- *EGLN1 (PHD2)*, *EGLN2 (PDH1)*
- *KIF1B*
- *IDH1*
- *MDH2*
- *EPAS1* encoding HIF2α
- *SLC25A11*
- *DMT3A*
- *DLST*
- *SUCLG2*

95% of the causative germline pathogenic variants are: *SDHx, VHL, RET, NF-1* (*MAX, TMEM127*)

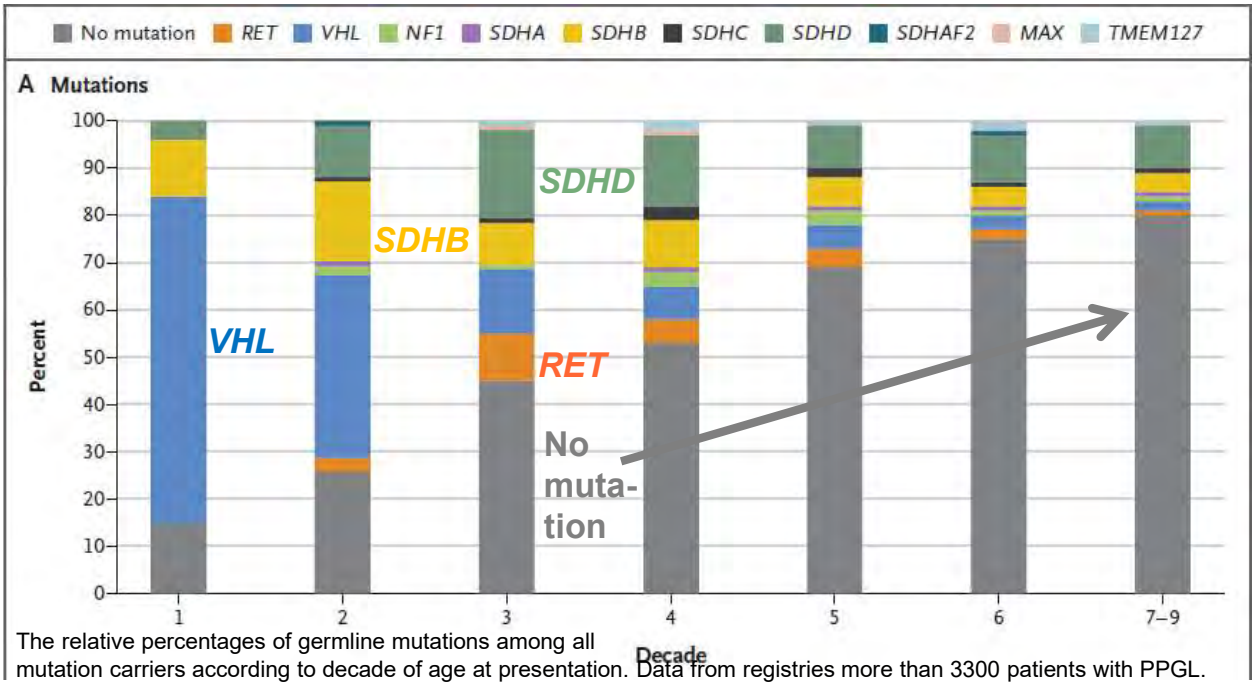
Kinase Signaling Pathway – "Cluster 2" (Adrenergic):

- ***RET***
- ***NF-1***
- *MAX*
- *TMEM127*
- *HRAS*

Wnt Signaling Pathway – "Cluster 3" (Noradrenergic/Adrenergic):

- *CSDE1*
- *MAML3* and *UBTF::MAML3* fusions

51



The relative percentages of germline mutations among all mutation carriers according to decade of age at presentation. Data from registries more than 3300 patients with PPGL.

Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. *N Engl J Med*. 2019; 381(6):552-565.

52

Genetic Testing

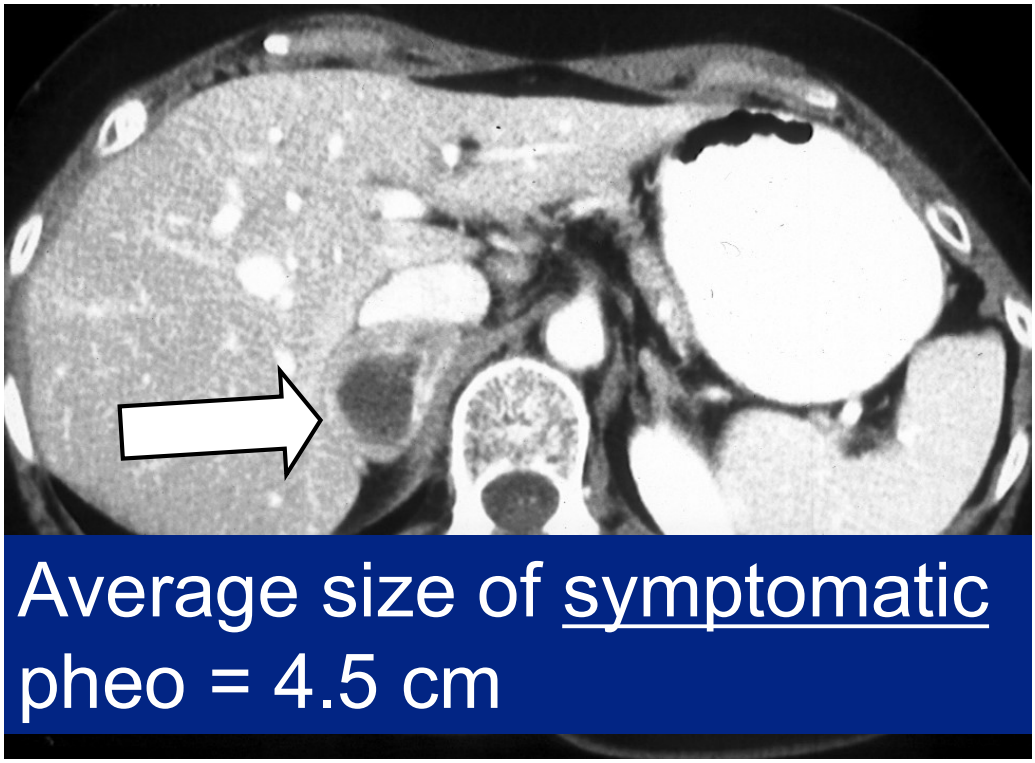
- ✓ 40% of patients with pheo/PGL have disease-causing germline mutations
- ✓ Hereditary pheo/PGL tumors typically present at a younger age than sporadic neoplasms
- ✓ **Genetic testing should be considered in and discussed with all patients**—especially if a patient has one or more of the following:
  1) PGL
  2) bilateral adrenal pheo
  3) unilateral adrenal pheo & + FHx of pheo/PGL
  4) unilateral adrenal pheo & young age (<60 y)
  5) other clinical findings suggestive of one of the syndromic disorders

53

Localization (1)

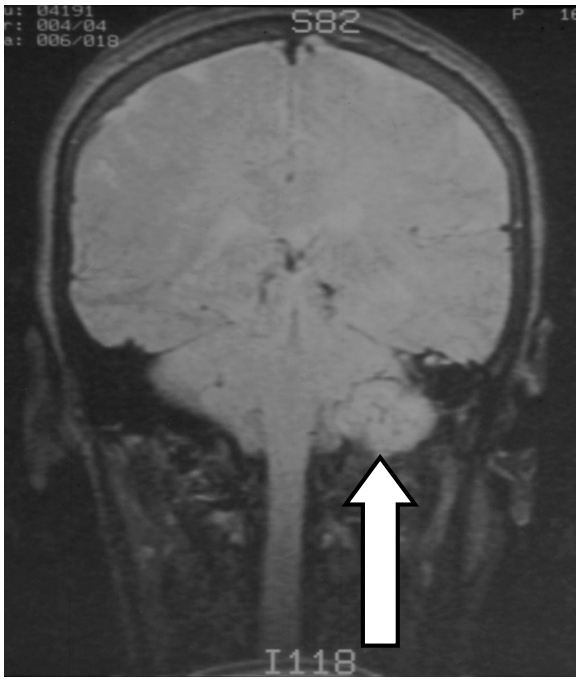
- We **usually** do not proceed with localization studies until biochemical studies have confirmed the dx of a catecholamine-secreting tumor
- Computer-assisted imaging of the adrenal glands abdomen with contrast-enhanced CT should be the first localization test (sensitivity, >95%; specificity, >65%)
- Approximately 85% of these tumors are found in the adrenal glands, and 95% are found in the abdomen and pelvis

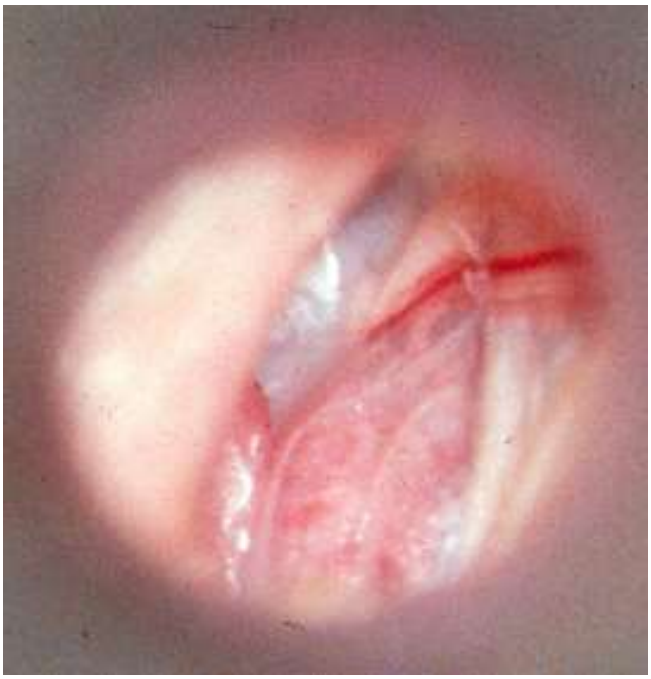
54



55

Parasympathetic PGL: Jugulotympanic





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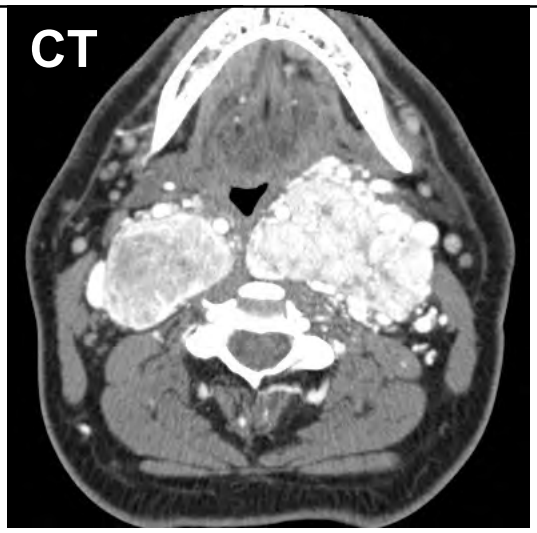
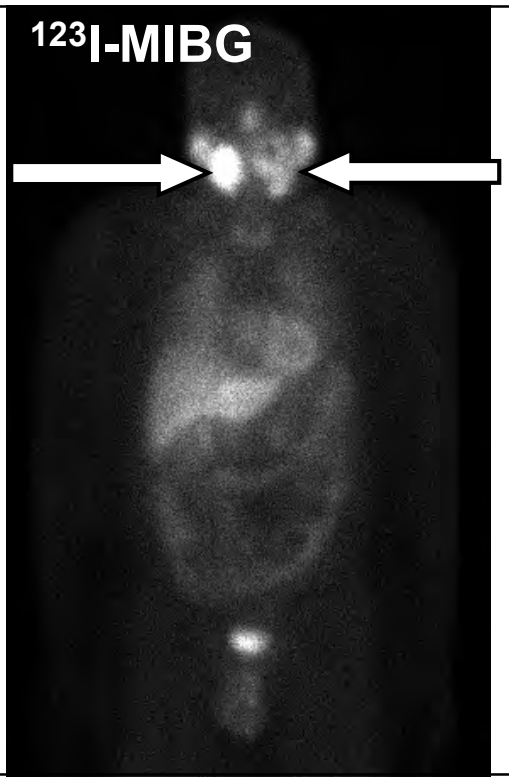
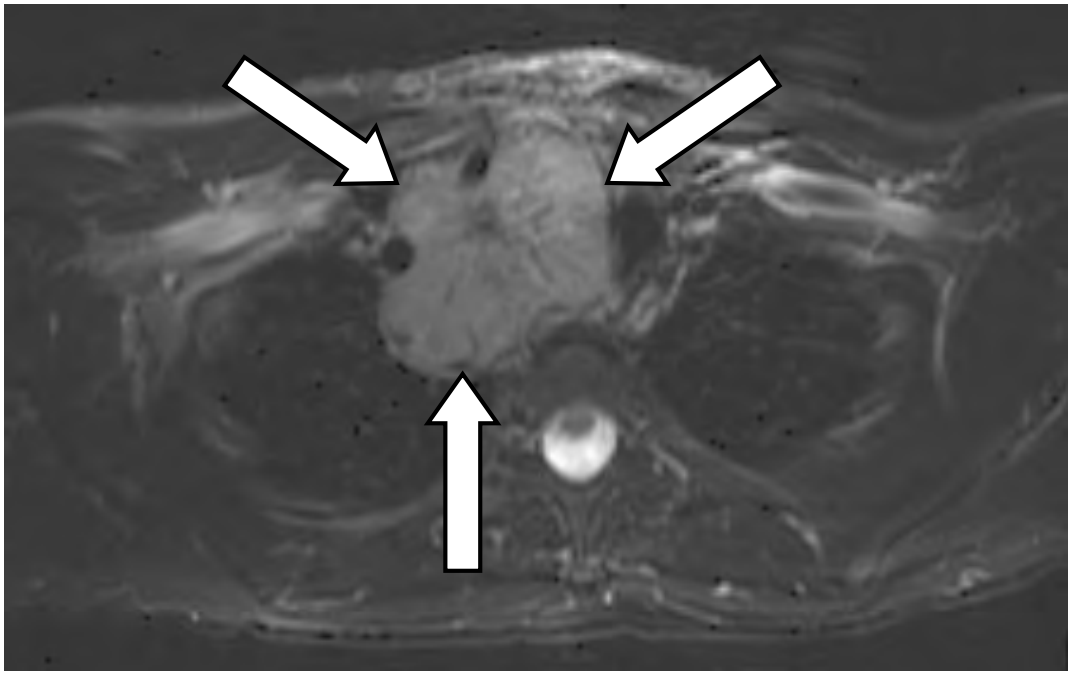




Parasympathetic PGL:
Carotid Body
Bilateral

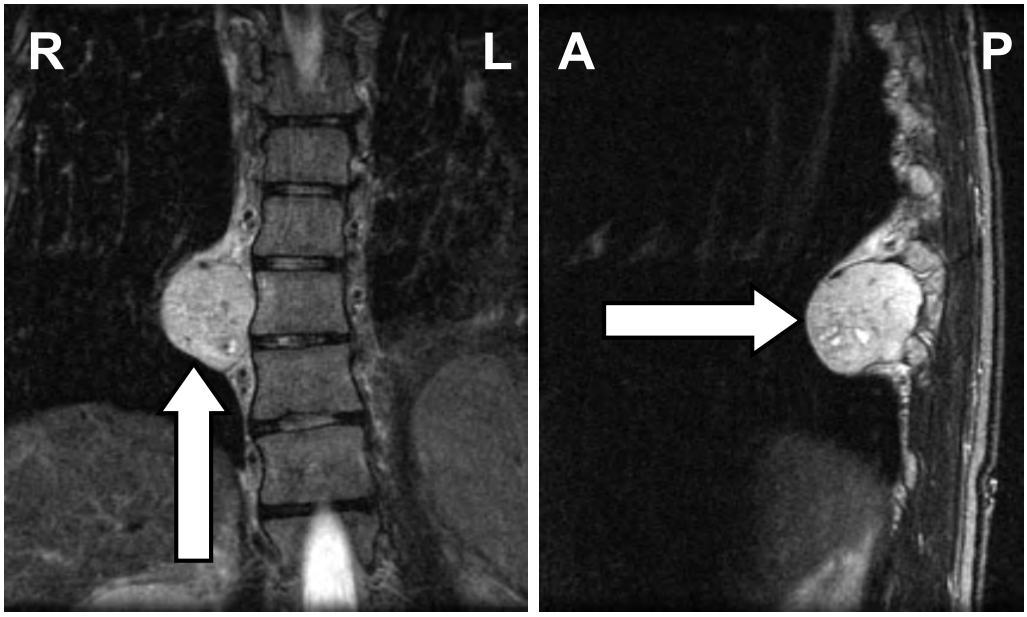
57

Parasympathetic PGL: Upper Mediastinum



58

Sympathetic PGL: Posterior Mediastinum



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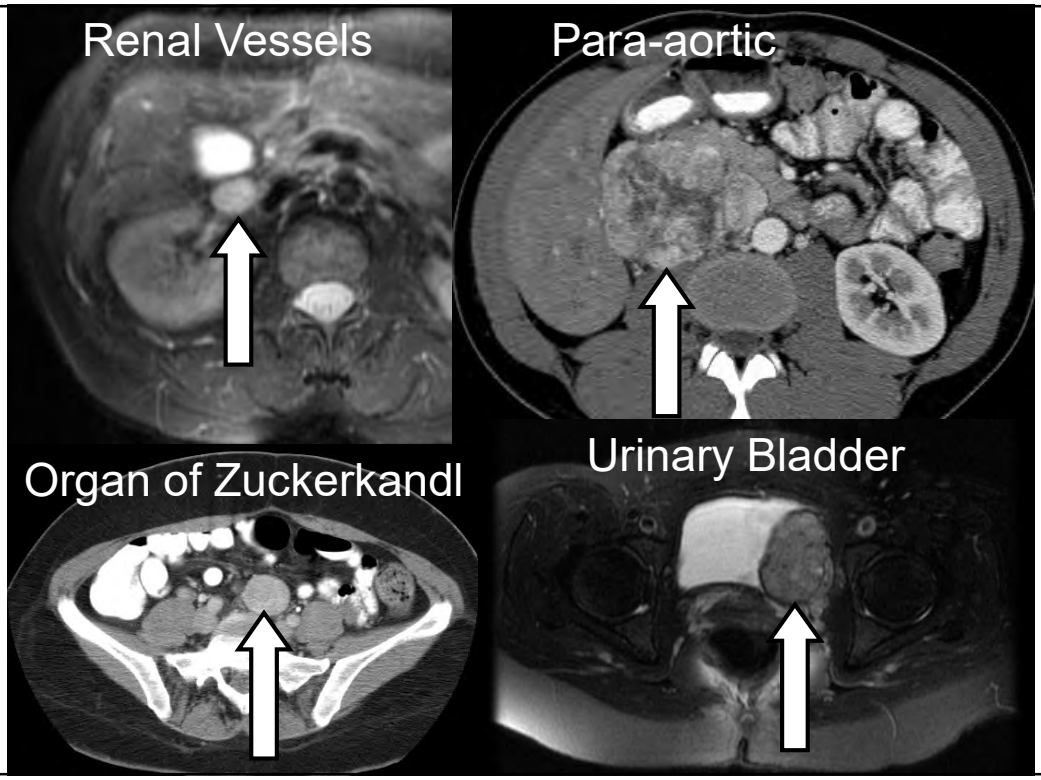


60

Common Sense Tips on Localization

- ✓ The tumor can always be found in the symptomatic pt with pheo—the avg diameter is 4.5 cm. **If you are having trouble localizing a pheo, it is usually because your patient does not have a pheo & you have ignored some of the biochemical dx tips**
- ✓ MRI is over-rated
- ✓ EPI/metanephrine-predominant tumors will "always" be localized to the adrenal medulla
- ✓ NE/normetanephrine-predominant tumors may arise from the adrenal medulla or from sympathetic paraganglioma in the abd, pelvis, chest, or neck

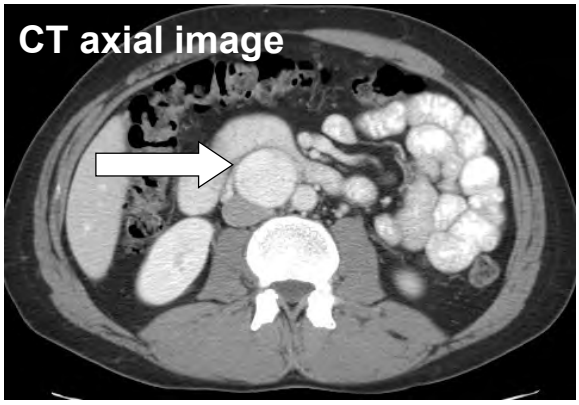
61

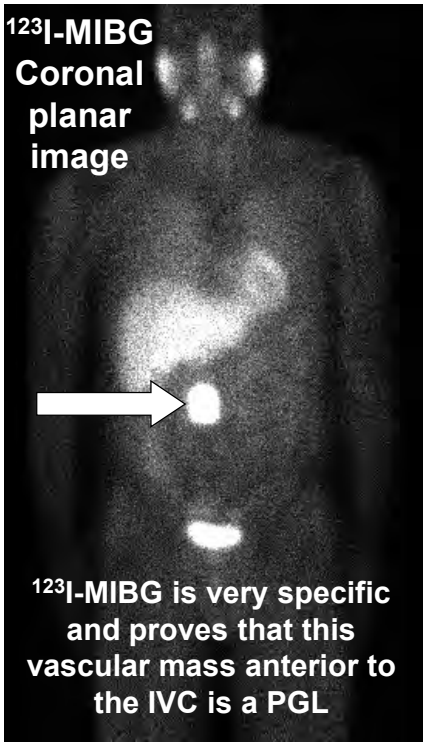
Localization (2)

- Ga-68 DOTATATE PET CT or FDG-PET CT or 123-I-metaiodobenzylguanidine (MIBG) scintigraphy are indicated if abdominal imaging is neg or if you are looking for additional PGLs or **metastatic disease**

62

The historical molecular imaging reference standard: ^{123}I-metaiodobenzylguanidine (MIBG) combined with anatomic imaging with CT or MRI





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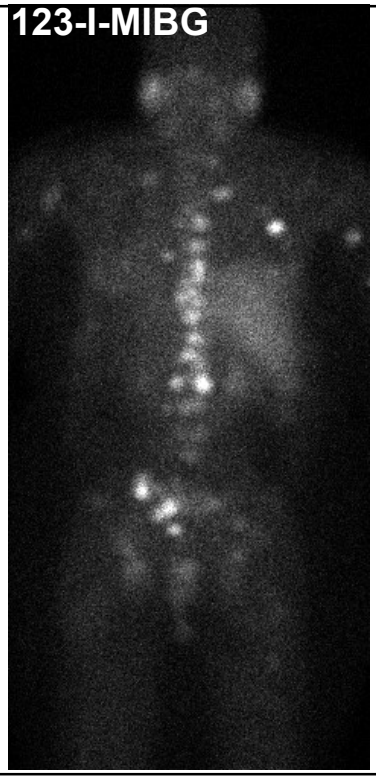
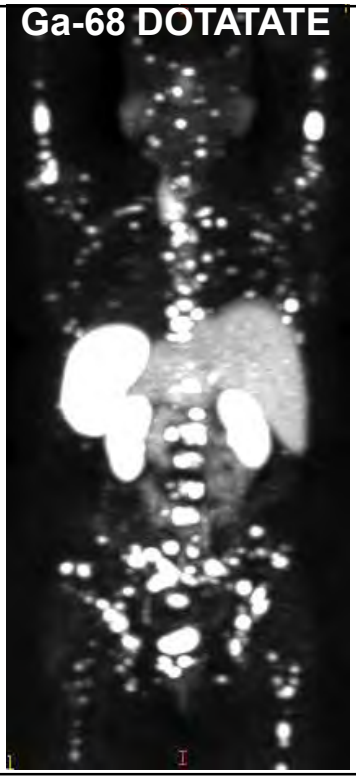


Same patient, same time frame

Although specific, 123-I-MIBG lacks sensitivity



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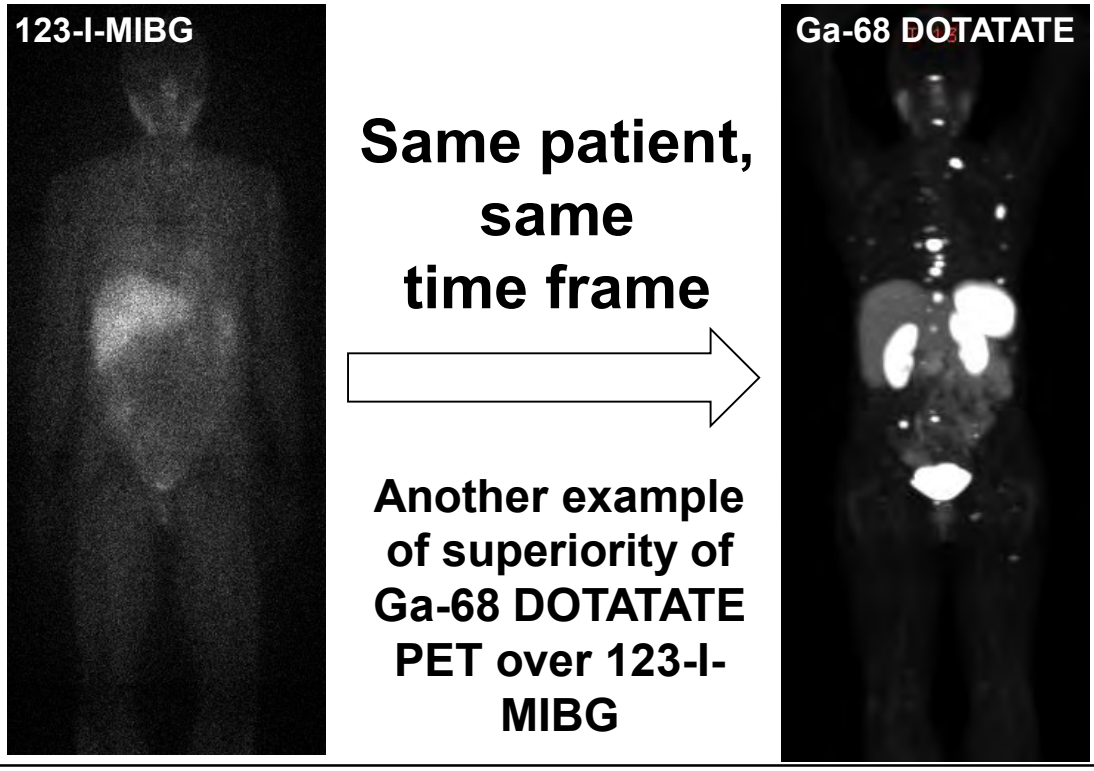

65

Localization (2)

- Ga-68 DOTATATE PET CT or FDG-PET CT or 123-I-metaiodobenzylguanidine (MIBG) scintigraphy are indicated if abdominal imaging is neg or if you are looking for additional PGLs or metastatic disease
- **If a typical (<8 cm) unilateral adrenal pheo is found on CT or MRI, nuclear imaging is superfluous and may even confuse the clinician**
- **If the adrenal pheo is >8-cm in diameter or if a PGL is found, then 68-Ga-DOTATATE PET, FDG-PET, or 123-I-MIBG scintigraphy are indicated because the pt has ↑ed risk of malignant disease or additional PGLs**

66

Treatment (1)

- ✓ Combined α- and β-adrenergic blockade is one approach to control BP & prevent intraop hypertensive crises
- ✓ We start α-adrenergic blockade with doxazosin 7 to 10 days preop to normalize BP & expand contracted blood volume
- ✓ BP should be monitored 2x/d. Target BP is <120/80 mm Hg (seated), with SBP >90 mm Hg (standing); both targets should be modified on basis of the patient's age and comorbid disease

Weingarten TN, et al. Preoperative Levels of Catecholamines and Metanephrines and Intraoperative Hemodynamics of Patients Undergoing Pheochromocytoma and Paraganglioma Resection. *Urology*. 2017;100:131-138.

67

Treatment (1)

- ✓ Combined α- and β-a
  approach to control B
  hypertensive crises
- ✓ We start α-adrenergi
  10 days preop to nor
  blood volume
- ✓ BP should be monito
  mm Hg (seated), with
  both targets should b
  patient's age and cor

NOTE: If patient is already on a β-B, don't stop it, simply add your α-adrenergic blocker

NOTE: Except for CCBs and β-Bs, stop other BP meds so that you can get on max doses of your α-blocker

NOTE: If you patient has normal BP, still α-adrenergic block—target low normal SBP for age and maximize dietary sodium

Weingarten TN, et al. Preoperative Levels of Catecholamines and Metanephrines and Intraoperative Hemodynamics of Patients Undergoing Pheochromocytoma and Paraganglioma Resection. *Urology*. 2017;100:131-138.

68

Treatment (2)

- ✓ On the second or third day of α-adrenergic blockade, pts are encouraged to start a diet high in sodium content (≥5,000 mg daily)
- ✓ This degree of volume expansion may be contraindicated in patients with CHF or renal insufficiency
- ✓ After adequate α-adrenergic blockade has been achieved, β-adrenergic blockade is initiated, which typically occurs 2 to 3 days preoperatively
- ✓ The last oral doses of α- & β-adrenergic blockers are given morning of surgery

69

Treatment (2)

- ✓ On the second c
  blockade, pts are encouraged to start a diet high in
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  insufficiency
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  achieved, β-adre
  typically occurs
- ✓ The last oral dos
  are given mornir

We block asymptomatic, normotensive patients too

We block biochemically silent pheochromocytomas too

If HR is <80 beats/min and BP controlled, you may not need a β-blocker

We have been using more doxazosin because of the ↑ cost of phenoxybenzamine—in that setting we frequently add a CCB to the doxazosin

70

Postop Follow-up (1)

- ✓ All pheochromocytomas & paragangliomas have malignant potential—ignore the pathology report that uses the word "benign"*
- ✓ 1 to 2 wks postop we measure fx cats mets in a 24-h urine or plasma fx mets
- ✓ If levels are normal, the resection of the pheo should be considered complete
- ✓ ↑ed levels of cats & mets detected postop are consistent with residual tumor due to either a 2nd primary lesion or occult metastases

*Tischler AS, de Krijger RR, Gill A, Kawashima A, Kimura N, Komminoth P, Papathomas TG, Thopmmson LDR, Tissier F, Williams MD, Young WF: Phaeochromocytoma. In: **WHO Classification of Tumours of Endocrine Organs**. Edited by RV Lloyd, RY Osamura, G Kloppel, J Rosai, International Agency for Research on Cancer (IARC) Press, Lyon, FRANCE, 2017, pp 183-189.

71

Long-Term Postop Follow-up (2)

- 24-h urine fractionated cats & mets or plasma fractionated mets should be checked annually for **life** (metastatic disease can be detected as late as **50 yrs** after the operation*)
- Annual biochemical testing assesses for metastatic disease, tumor recurrence in the adrenal bed, or delayed appearance of multiple primary tumors
- Follow-up CT or MRI are not needed unless the mets/cats become elevated or if:
  a) the original tumor was associated with minimal catecholamine excess
  b) the patient has a PPGL germline mutation

*Hamidi O, et al. Malignant Pheochromocytoma and Paraganglioma: 272 Patients Over 55 Years. *J Clin Endocrinol Metab*. 2017;102:3296-3305.

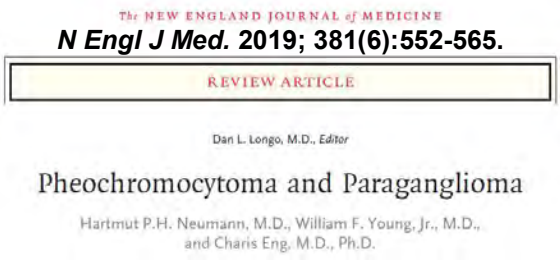
72

2024 Take Home Points:

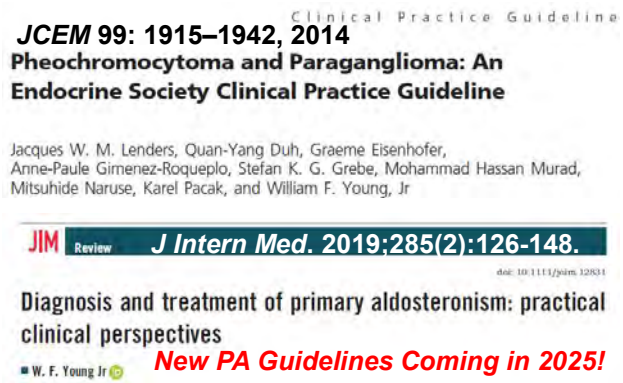
- **Primary aldosteronism:**
  - ✓It is common; most have normal serum K^+
  - ✓Test for it!! – Morning aldo & renin in "all" patients with ↑BP
  - ✓Don't worry about BP meds (eg, ARB, ACE-I, diuretics, MRAs)
  - ✓Don't trust CT
  - ✓Find or develop good AVS program & expert adrenal surgeon
- **Pheochromocytoma/paraganglioma:**
  - ✓It is rare
  - ✓Most positive case detection tests are false-positive **nor**metanephrine—know the drugs that interfere
  - ✓Incidental adrenal mass→rely on imaging phenotype
  - ✓MRI is over-rated

73

Reading



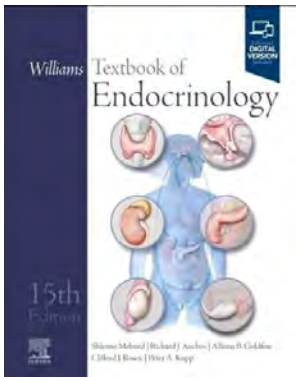
N Engl J Med. **2019; 381(6):552-565.**

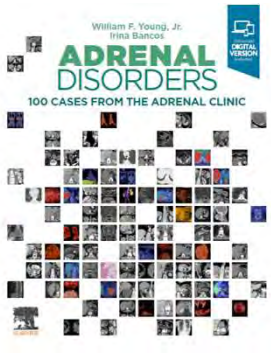


JCEM **99: 1915–1942, 2014**

New PA Guidelines Coming in 2025!

Endocrine Hypertension. In: Williams Textbook of Endocrinology, 15th Edition. 2025, Chap 14, pp 534-564





Adrenal Disorders: 100 Cases from the Adrenal Clinic, 1st Edition. Published 2022

74

Abbreviations used in this section:

- ACE-I, angiotensin converting enzyme inhibitor
- APA, aldosterone-producing adenoma
- ARB, angiotensin receptor blocker
- AVS, adrenal venous sampling
- ↑BP, hypertension
- CKD, chronic kidney disease
- EPL, eplerenone
- IHA, bilateral idiopathic hyperaldosteronism
- ↓K^+, hypokalemia
- PA, primary aldosteronism
- PAC, plasma aldosterone concentration
- PRA, plasma renin activity
- PRC, plasma renin concentration
- SPL, spironolactone

All abbreviations expanded on first usage

75

Abbreviations used in this section

- β-B, beta-blocker
- BP, blood pressure
- Catechols, catecholamines
- CCB, calcium channel blocker
- DA, dopamine
- DST, dexamethasone suppression test
- EPI, epinephrine
- HU, Hounsfield units
- ↑ed, increased
- Mets, metanephrines
- Mets, metanephrines
- MI, myocardial infarction
- MIBG, ^{123}I-metaiodobenzylguanidine
- NE, norepinephrine
- Normet, normetanephrine
- PGL, paraganglioma
- PPGL, pheochromocytoma and paraganglioma
- Pheo, pheochromocytoma
- TCA, tricyclic antidepressant

All abbreviations expanded on first usage

76