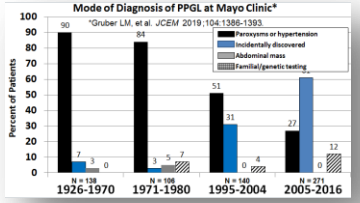
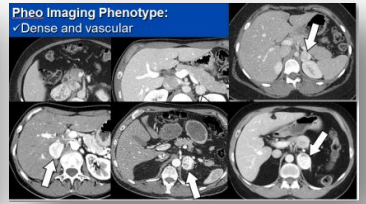
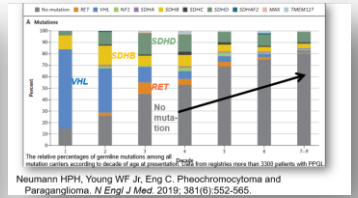
ENDOCRINE SOCIETY

13th ANNUAL BEST PRACTICE SERIES
ENDOCRINE SUMMIT, INDIA

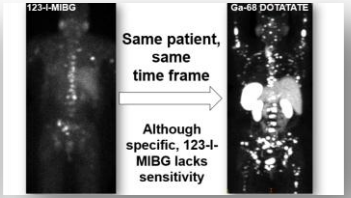
Update on Pheochromocytoma and Paraganglioma

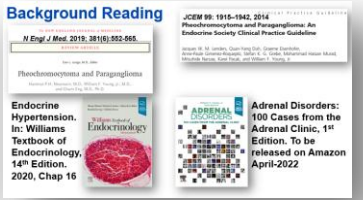






Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. *N Engl J Med*. 2019; 381(6):552-565.





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

Day 2 – 28th August – 2:00 – 2:45 PM

DISCLOSURE*

William F. Young, Jr., MD, MSc

Has no relevant financial relationships

Off Label Usage: None

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

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**

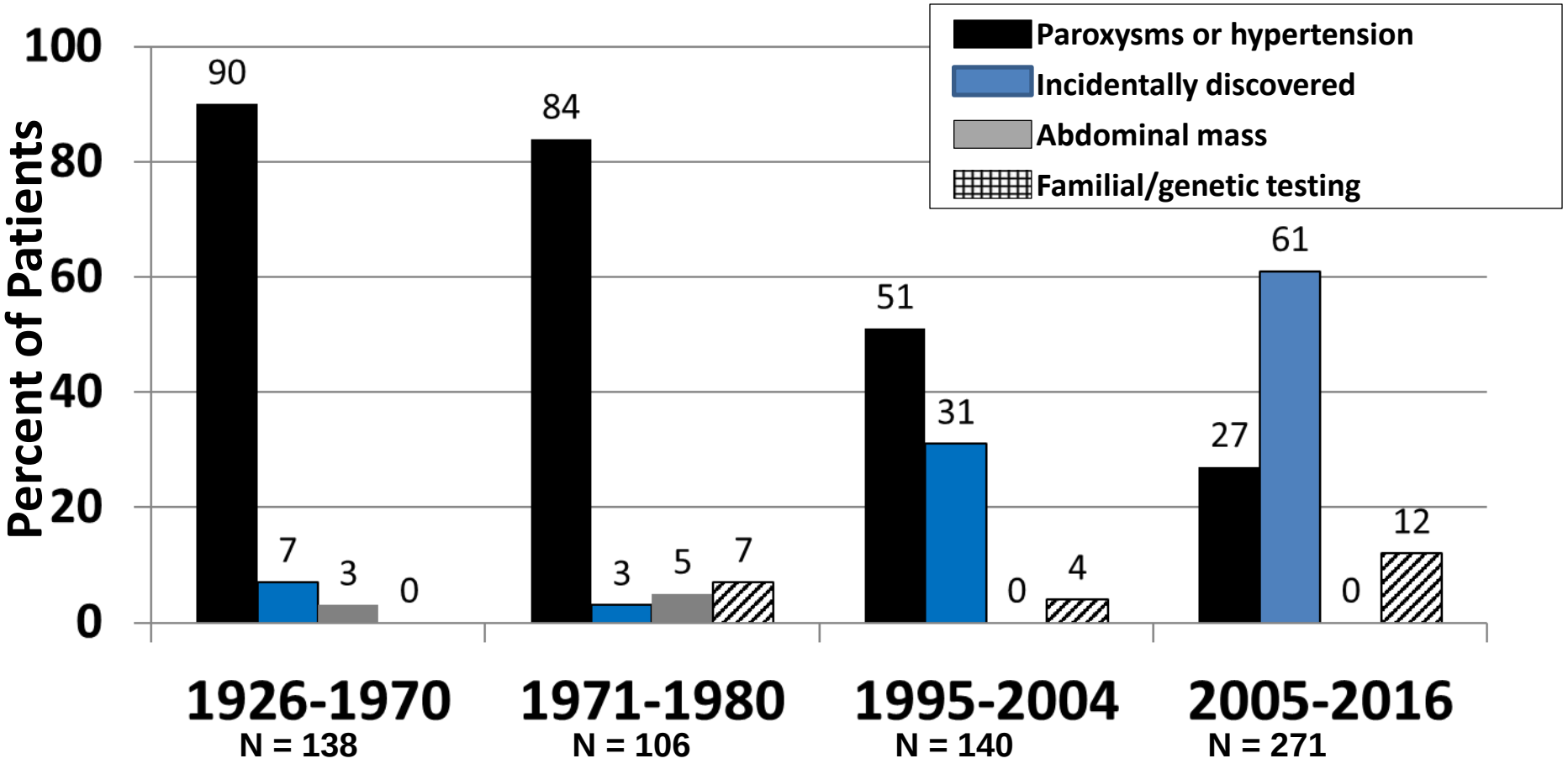
Pheo: Clinical Presentation

- ✓ **Prevalence** -- 0.01% to 0.1%
- ✓ **Occurrence** -- equally in men and women, primarily in the 3rd through 5th decades
- ✓ **Symptoms** – in 2022 symptoms are present in <50% of patients
- ✓ **Mode of Diagnosis** – has changed dramatically over the past 100 yrs—60% are discovered as adrenal incidentalomas

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

Mode of Diagnosis of Pheochromocytoma at Mayo Clinic*

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



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.

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.

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

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- ✓ 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!

However, 60% of pheochromocytoma patients in 2022 are detected as adrenal incidentalomas!

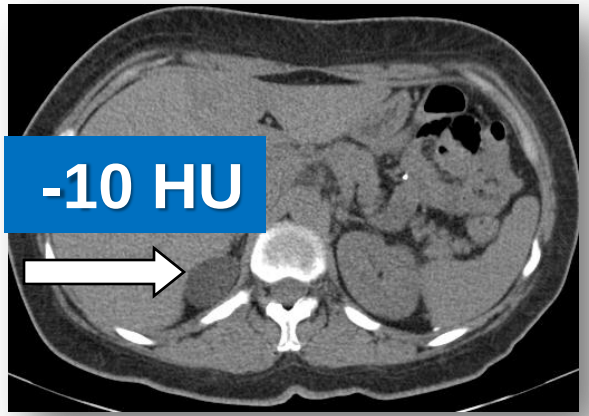
When small (<1.5 cm), pheochromocytomas are not large enough to make enough catechols to be biochemically detectable AND some pheos are nonfunctional

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

“Imaging Phenotype”

CT attenuation measured in Hounsfield Units (HU)

Precontrast radiodensity <10 HU

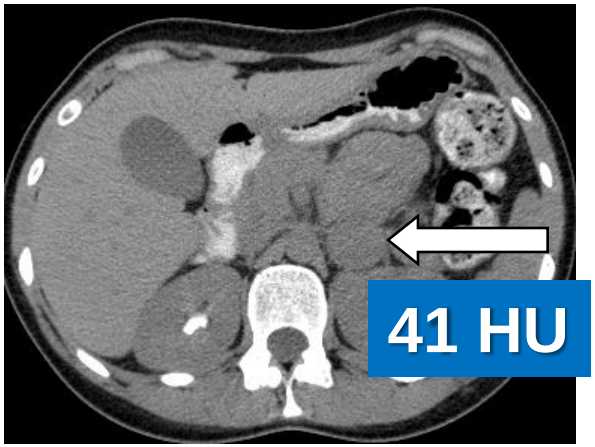


More lipid

Benign

-20 HU

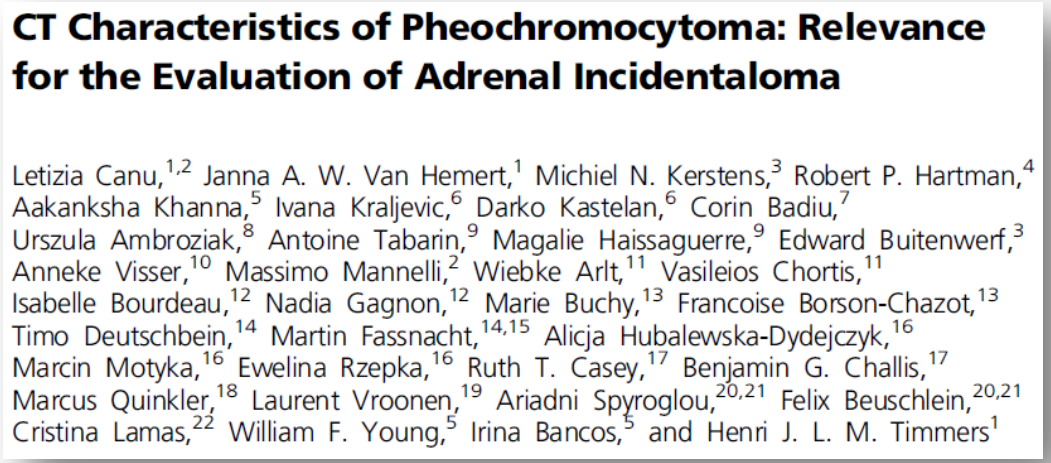
+60 HU



Less lipid

ACC
Met
Pheo
Lipid-poor adenoma

Precontrast radiodensity >20 HU



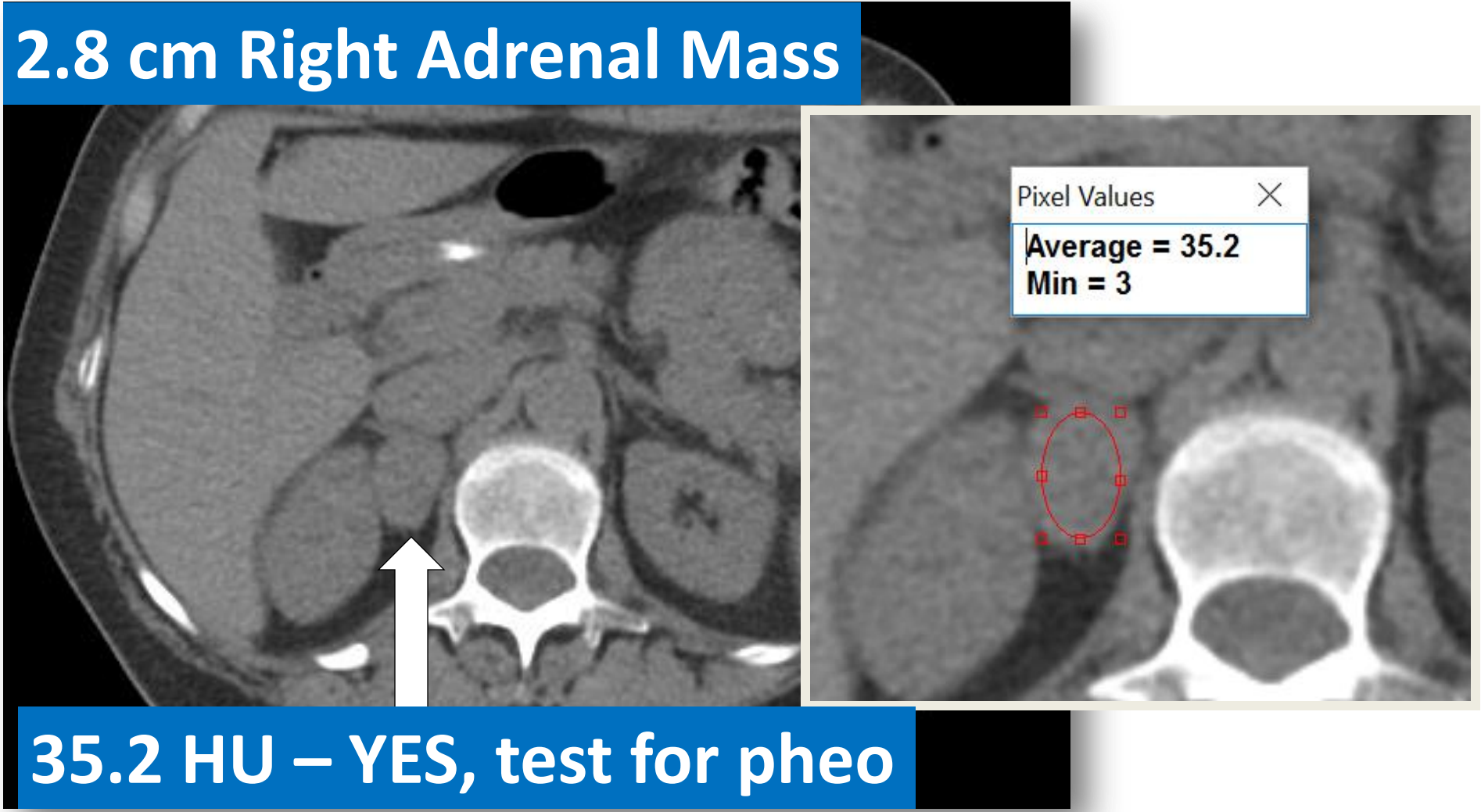
CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma

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

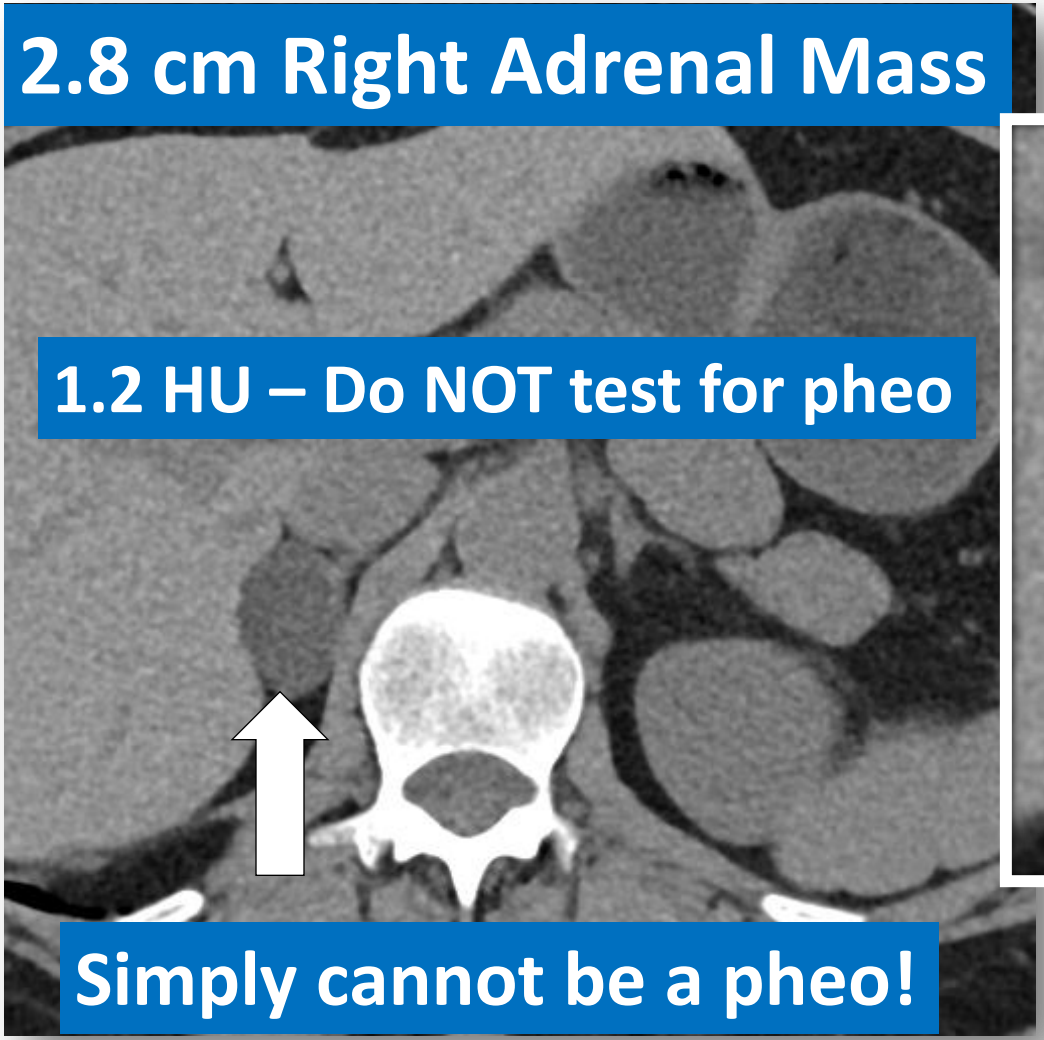
Canu L, et al. CT Characteristics of Pheochromocytoma: Relevance for the Evaluation of Adrenal Incidentaloma. *J Clin Endocrinol Metab*. 2019;104(2):312-18

2.8 cm Right Adrenal Mass



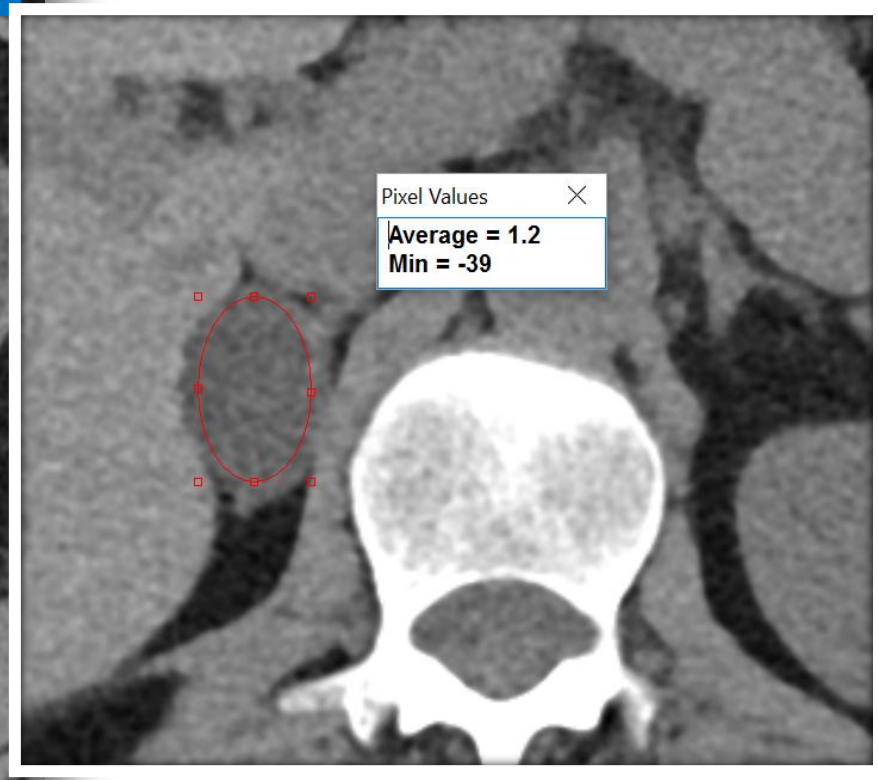
35.2 HU – YES, test for pheo

2.8 cm Right Adrenal Mass

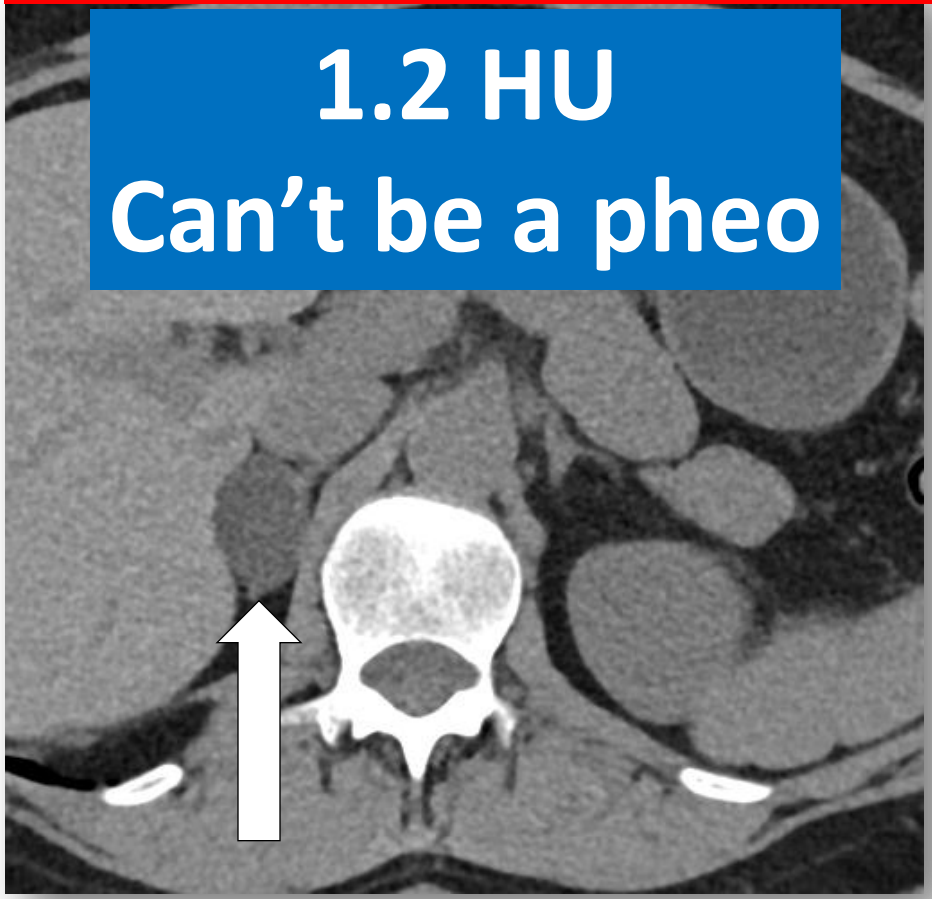


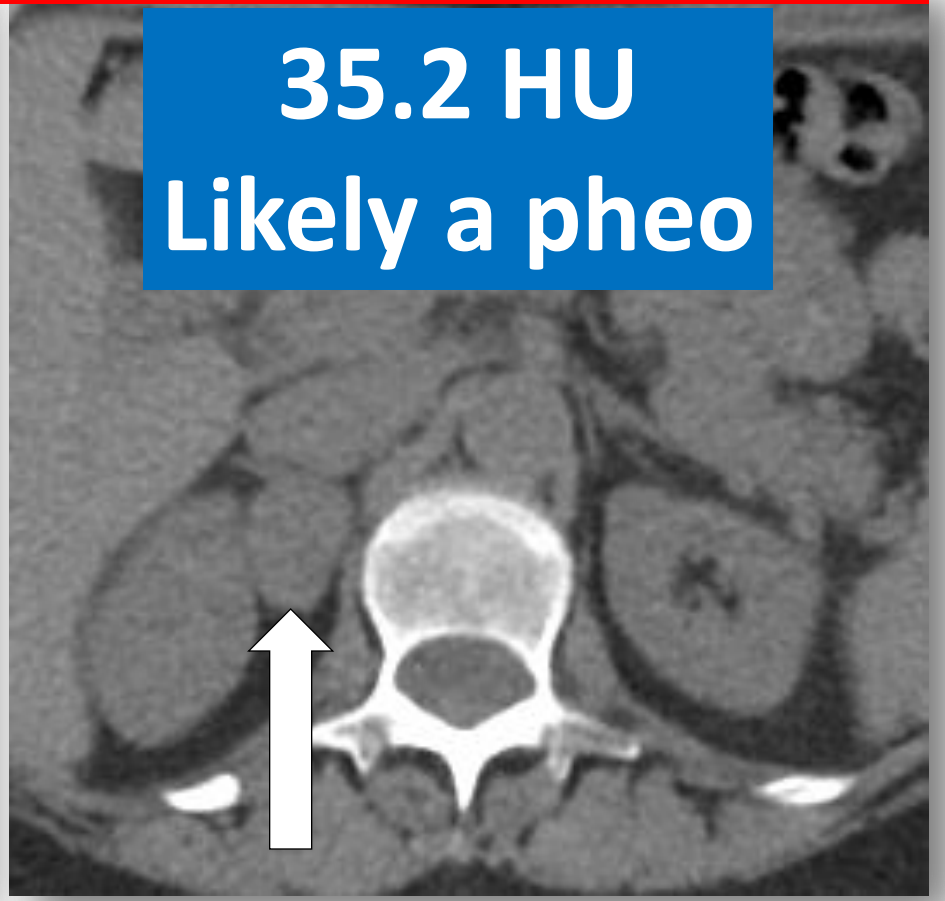
1.2 HU – Do NOT test for pheo

Simply cannot be a pheo!



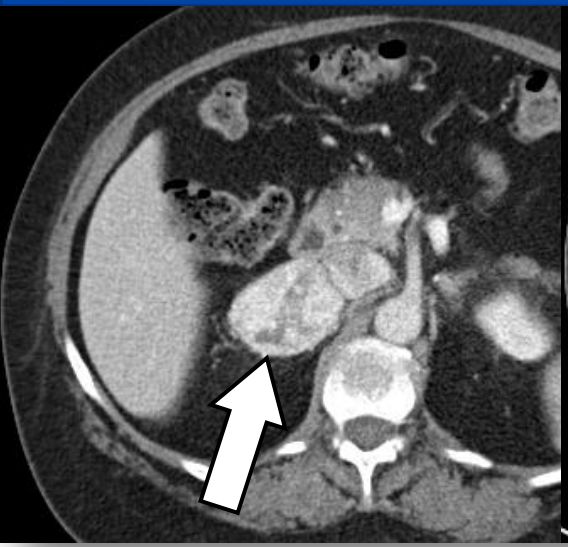
<10 HU = do NOT screen for pheo

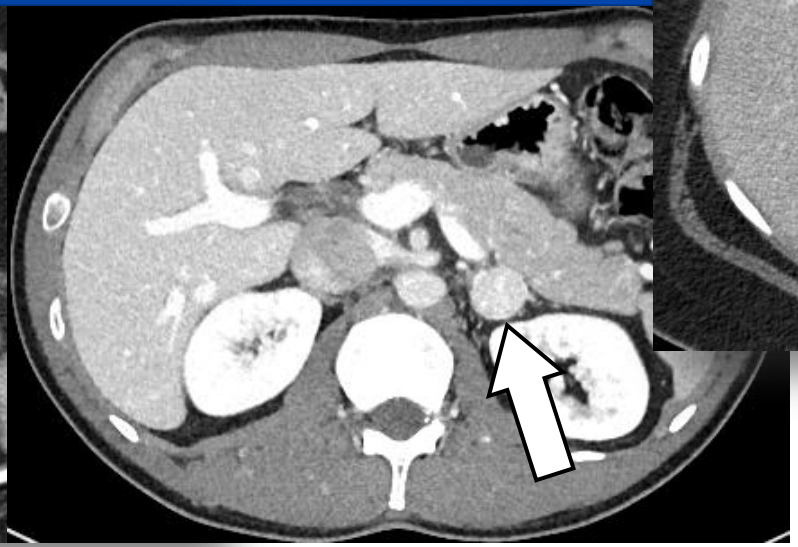


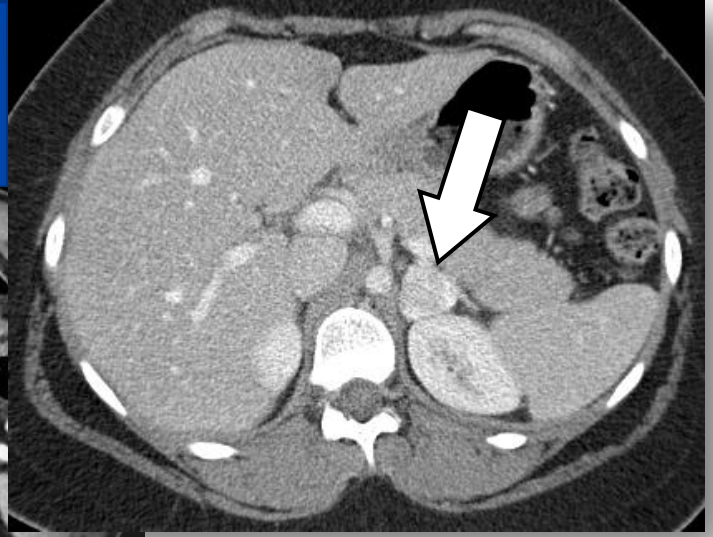


Pheo Imaging Phenotype:

✓Dense and vascular







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.

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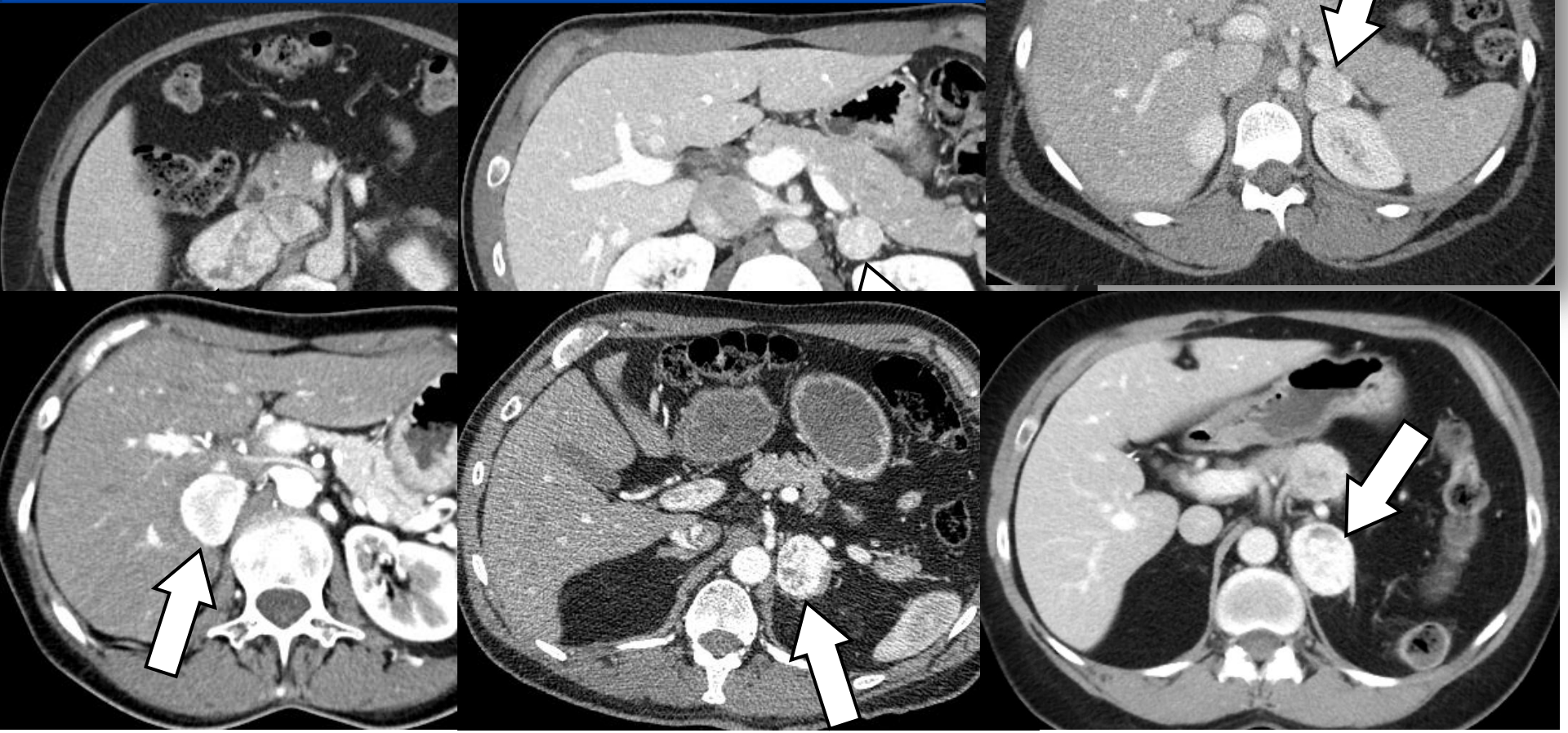
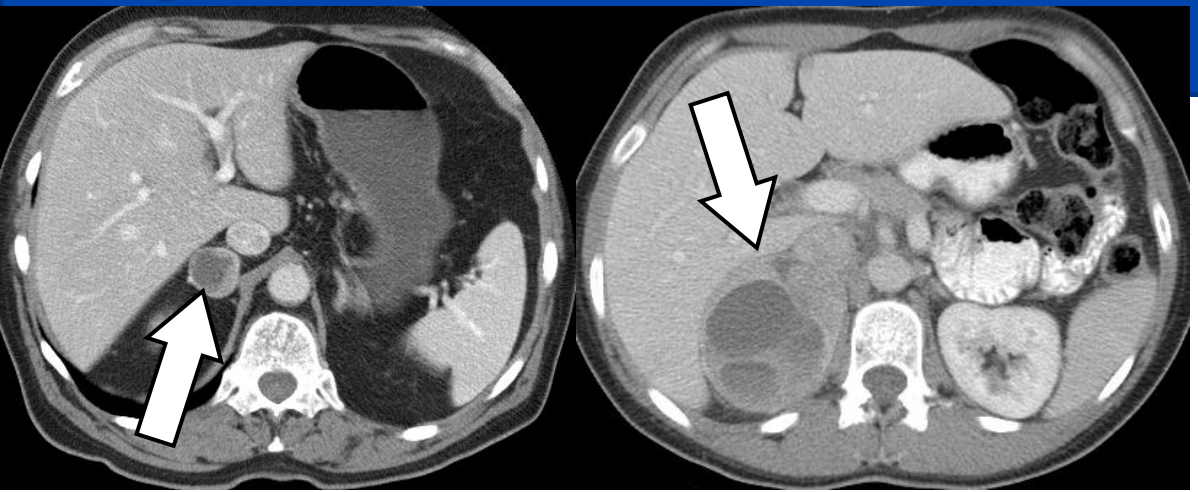
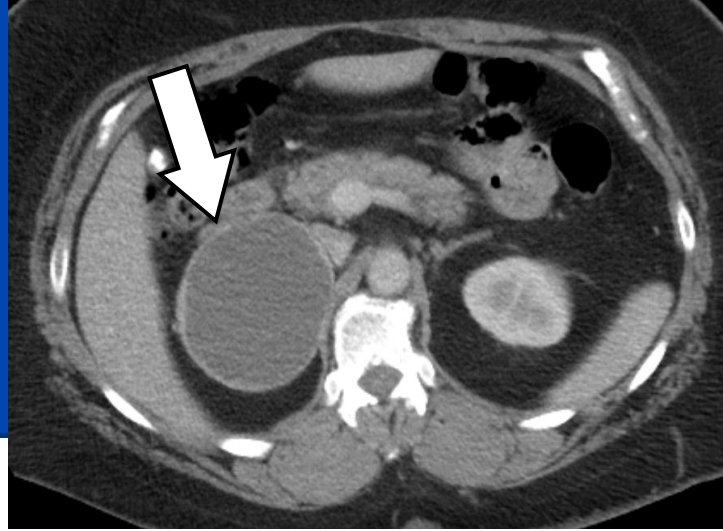


Pheo Imaging Phenotype:

- ✓Dense and vascular
- ✓Inhomogeneous with cystic degenerative areas—BEWARE of

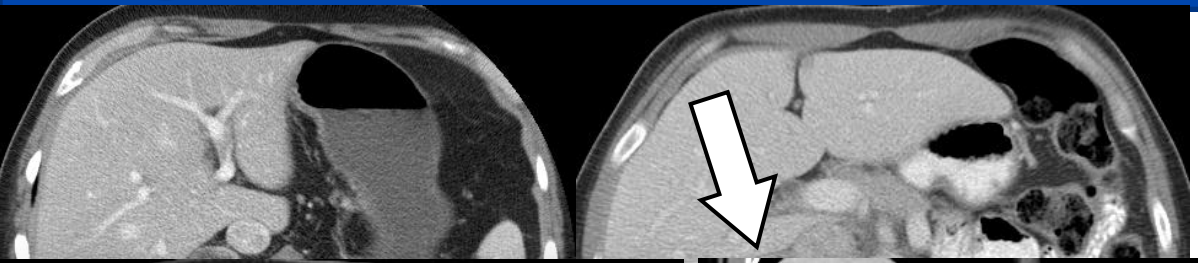


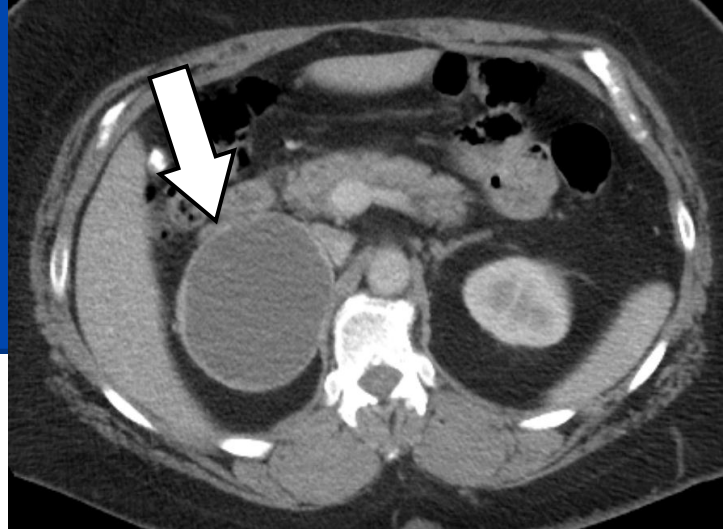


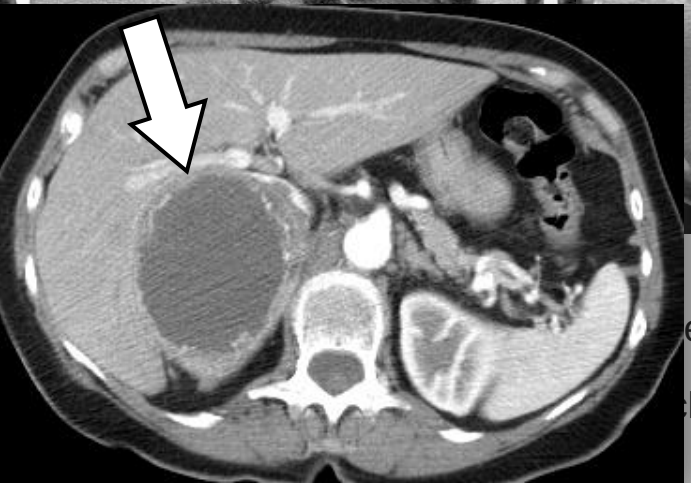
Dogra P, Navin PJ, McKenzie TJ, Foster T, Dy B, Lyden M, Young WF Jr, Bancos I. Clinical, imaging and biochemical presentation of cystic pheochromocytomas. *Clin Endocrinol (Oxf).* 2022 Apr 21. doi: 10.1111/cen.14743. Epub ahead of print. PMID: 35445428.

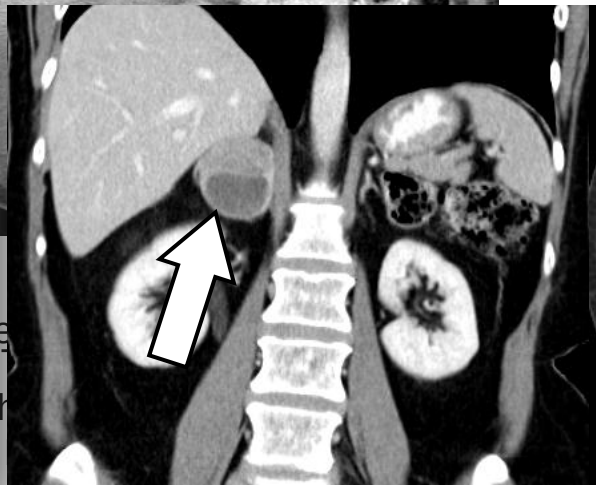
Pheo Imaging Phenotype:

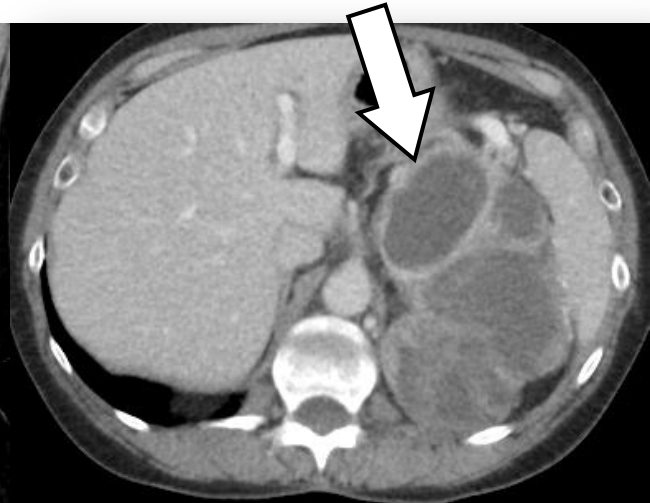
- ✓Dense and vascular
- ✓Inhomogeneous with cystic degenerative areas





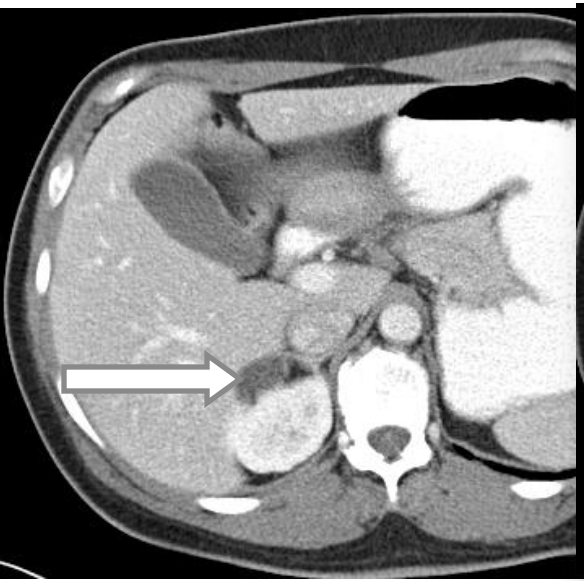


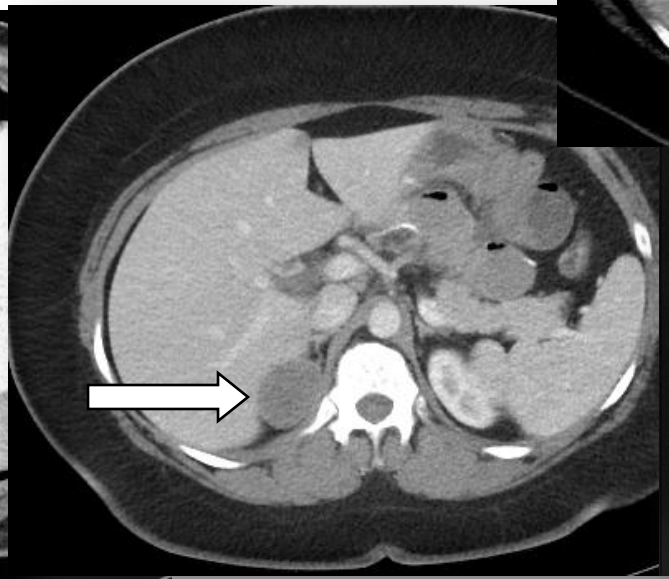


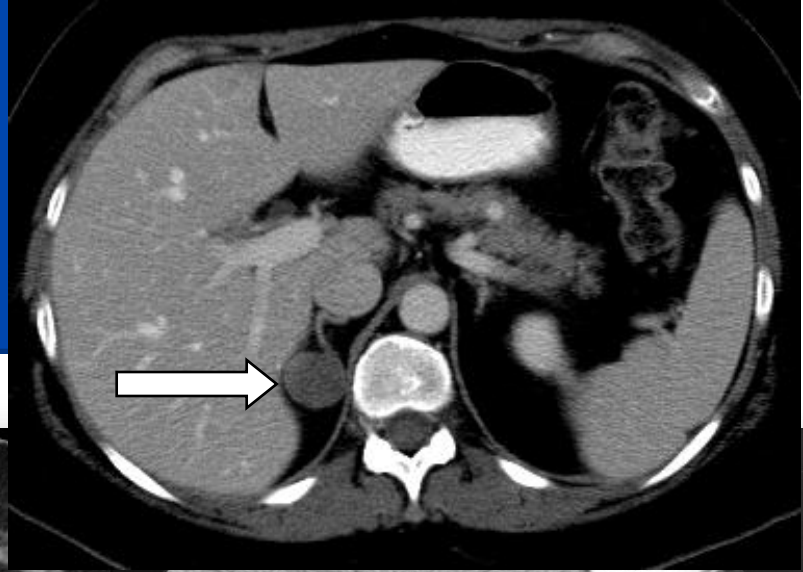


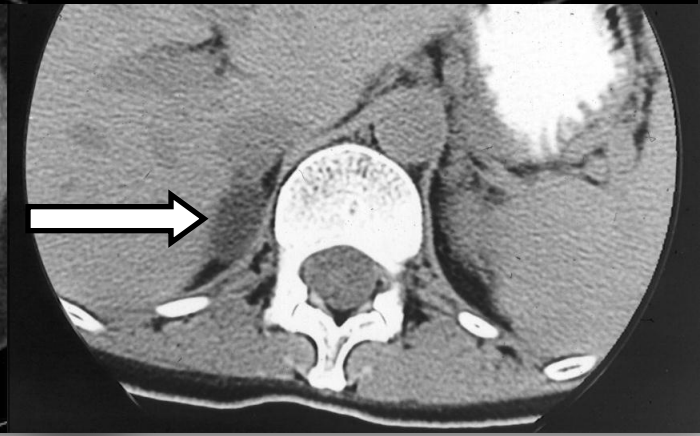
Adenoma Imaging Phenotype:

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





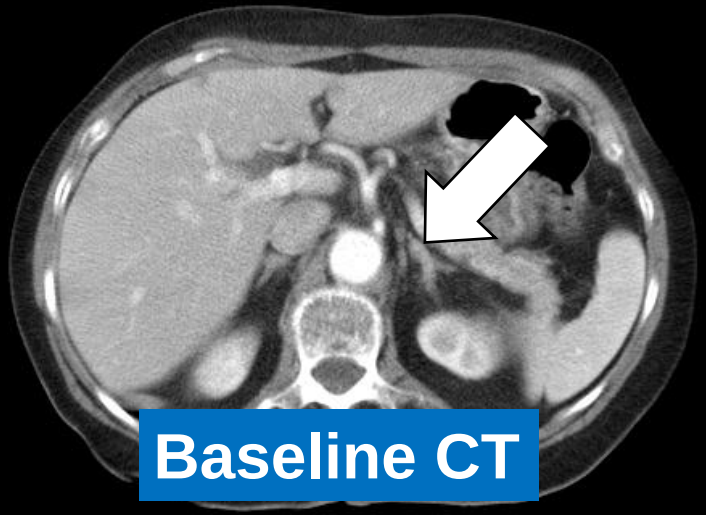


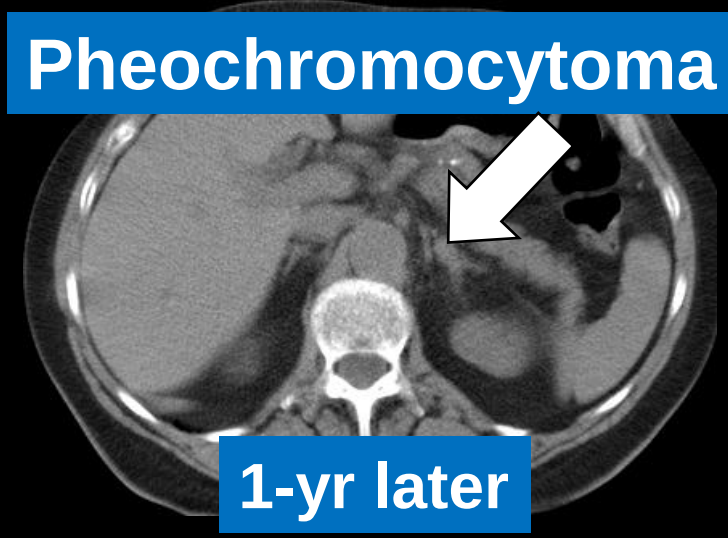


Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med*. 2007 Feb 8;356(6):601-10. Review. PubMed PMID: 17287480.

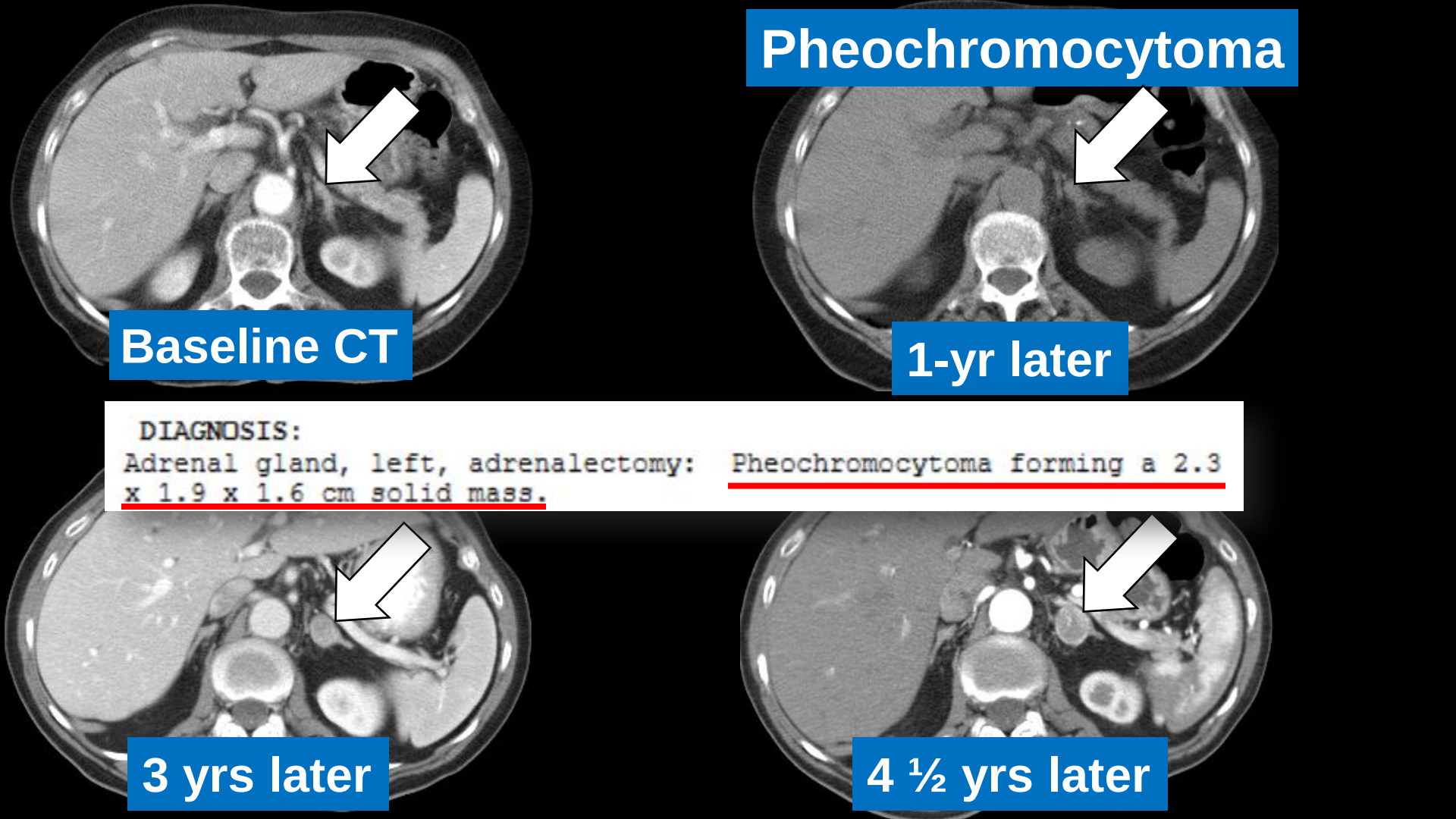
The Messages Here are Simple:

- 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

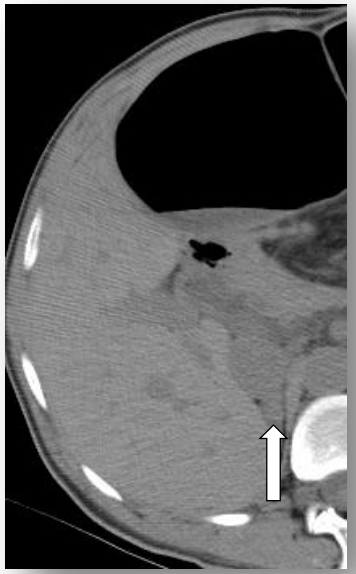




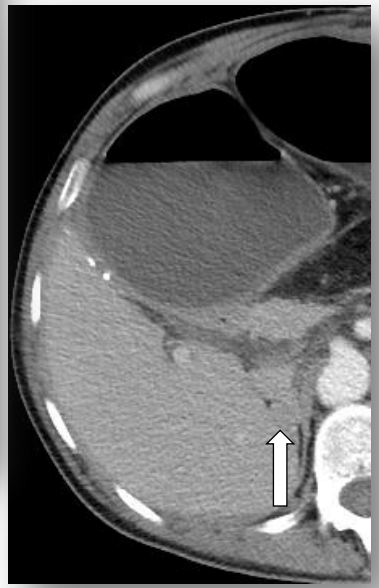
Pheochromocytomas don’t just “suddenly appear”—they grow slowly:
0.5 to 1 cm in diameter/yr


Pheochromocytoma
Baseline CT
1-yr later
DIAGNOSIS:
Adrenal gland, left, adrenalectomy: Pheochromocytoma forming a 2.3 x 1.9 x 1.6 cm solid mass.
3 yrs later
4 ½ yrs later

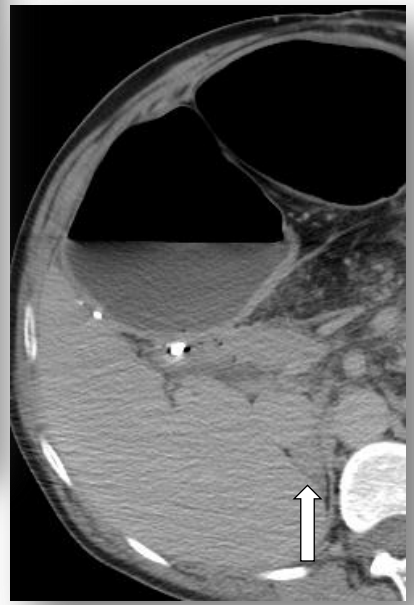
16 yrs of serial abdominal CTs



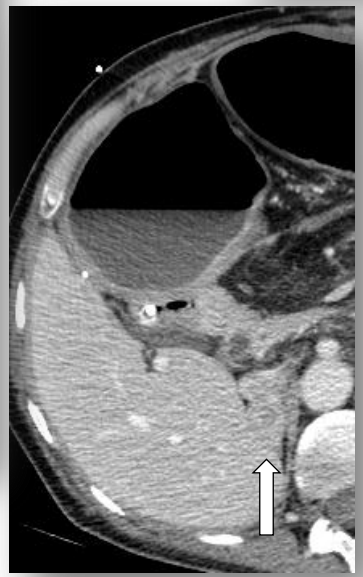
2005



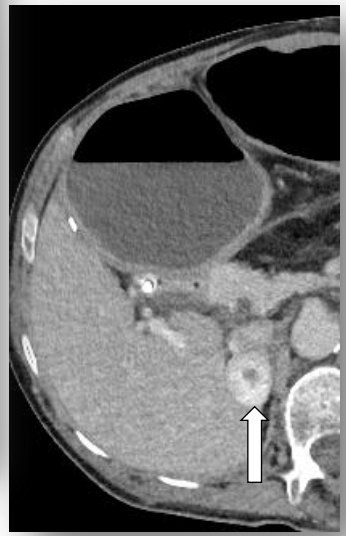
2009



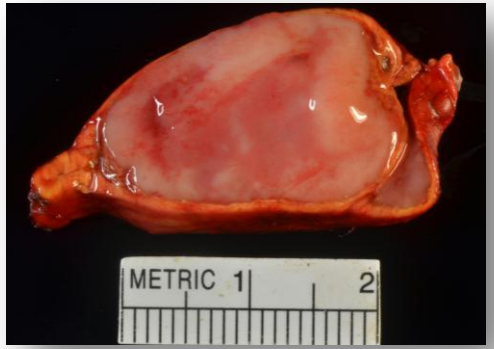
2014



2017



2021

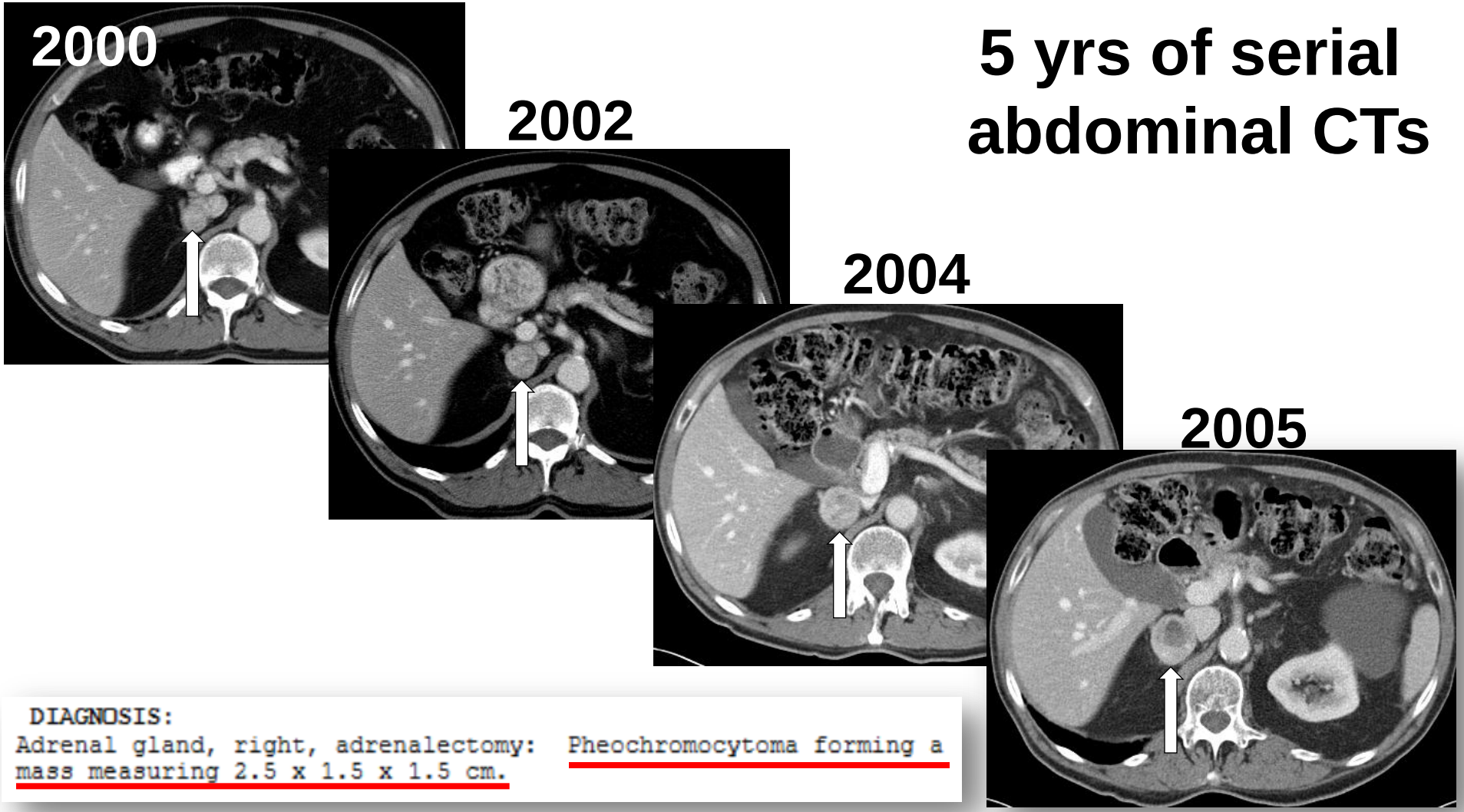


A. Adrenal gland, right, adrenalectomy: Pheochromocytoma, 4.4 cm in greatest dimension, confined to the adrenal gland. Ganglion cells are noted in the tumor but no definite neuronal component.

8 yrs of serial lumbar spine MRIs

DIAGNOSIS:
A. Adrenal gland, left, adrenalectomy: Pheochromocytoma (4.1 cm in greatest dimension).

5 yrs of serial abdominal CTs



DIAGNOSIS:
Adrenal gland, right, adrenalectomy: Pheochromocytoma forming a mass measuring 2.5 x 1.5 x 1.5 cm.

One Last Pearl on Diagnosis:

- In a patient with **spells**, the degree of ↑ of fractionated metanephrines and catecholamines 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)

Genetic Causes

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

- ***SDHx: SDHA, SDHAF2, SDHB, SDHC, SDHD***
- ***VHL***
- *FH*
- *HIF2α*
- *EGLN1 (PHD2), EGLN2 (PDH1)*
- *KIF1B*
- *IDH1*
- *MDH2*
- *EPAS (1,2)*
- *SLC25A11*
- *DMT3A*

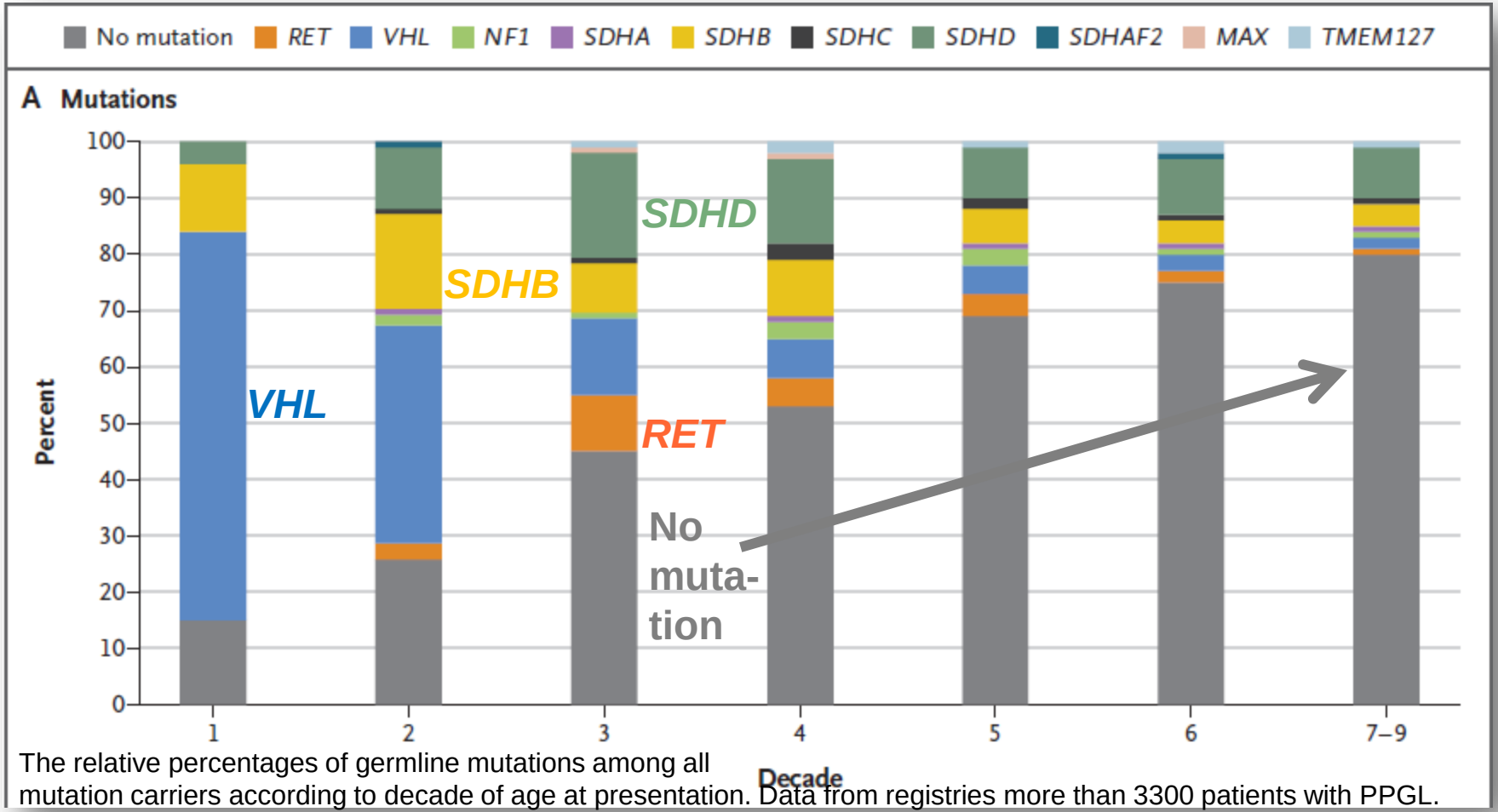
95% of the causative germline pathogenic variants are: *SDHx, VHL, RET, NF-1* (*MAX, TMEM127*)

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

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

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

- *CSDE1*
- *MAML3*



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.

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

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

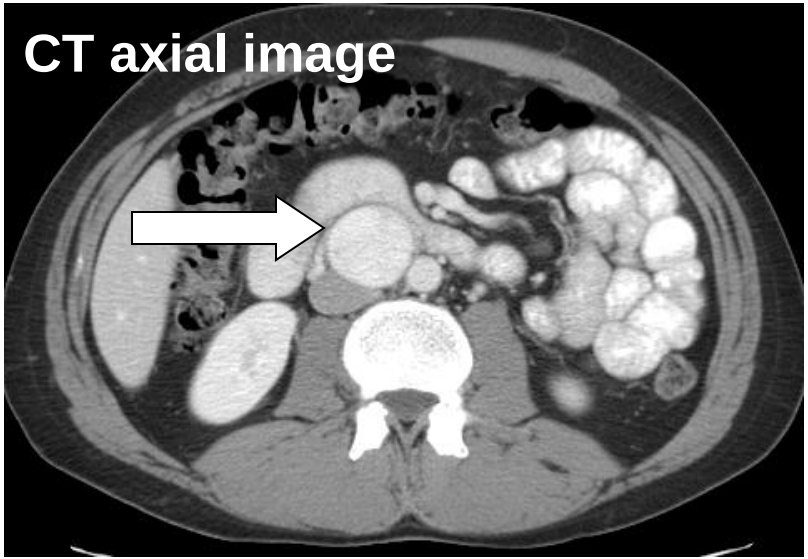
Common Sense Tips on Localization

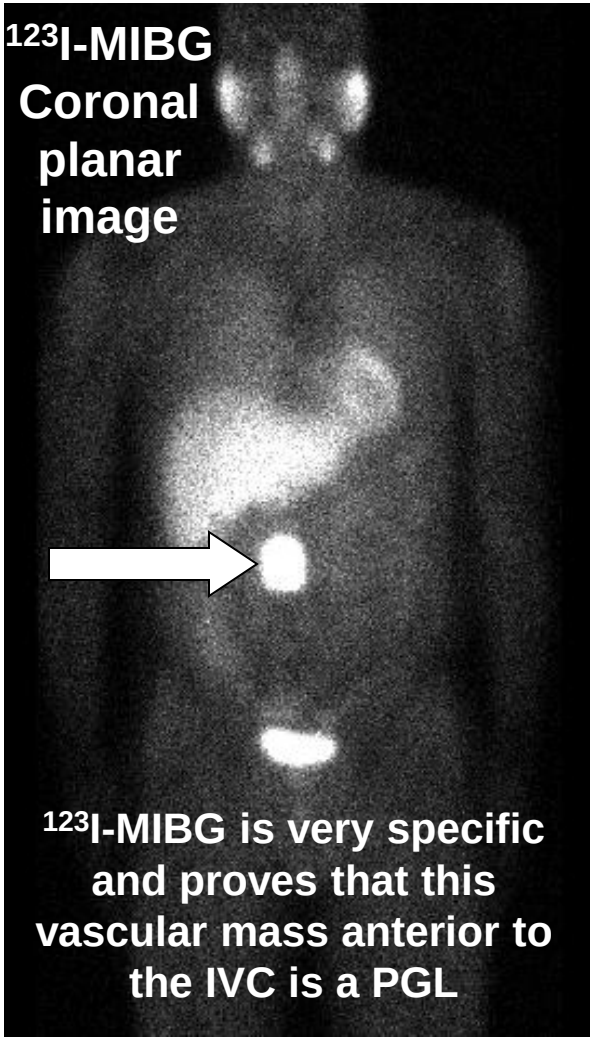
- ✓ The tumor can always be found in the sx pt with pheo—the avg diameter is 4.5 cm. **If you are having trouble localizing a pheo, it is usually because your pt does not have a pheo & you have ignored some of the biochemical dx tips**
- ✓ MRI is over-rated
- ✓ EPI/metanephrine-predominant tumors will “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

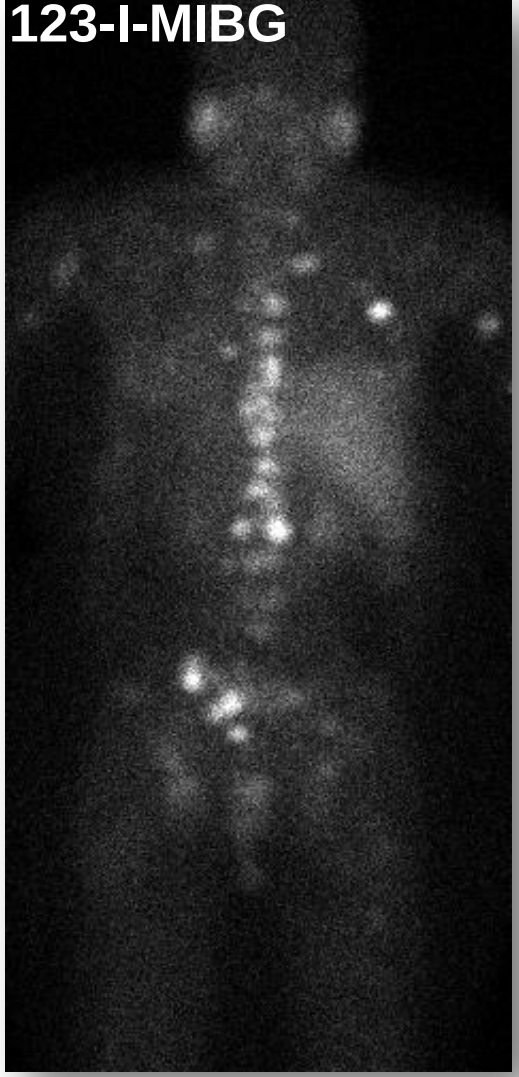
Localization (2)

- 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**

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

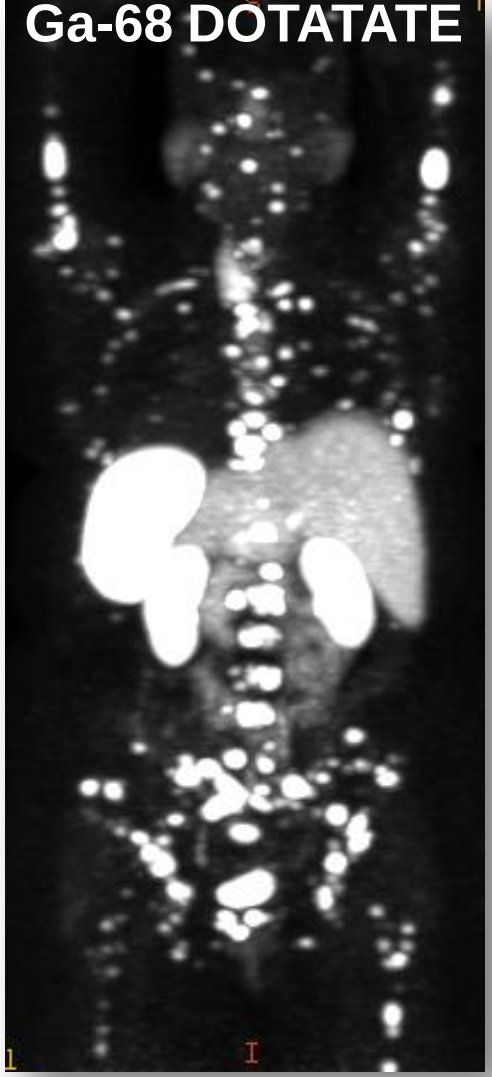


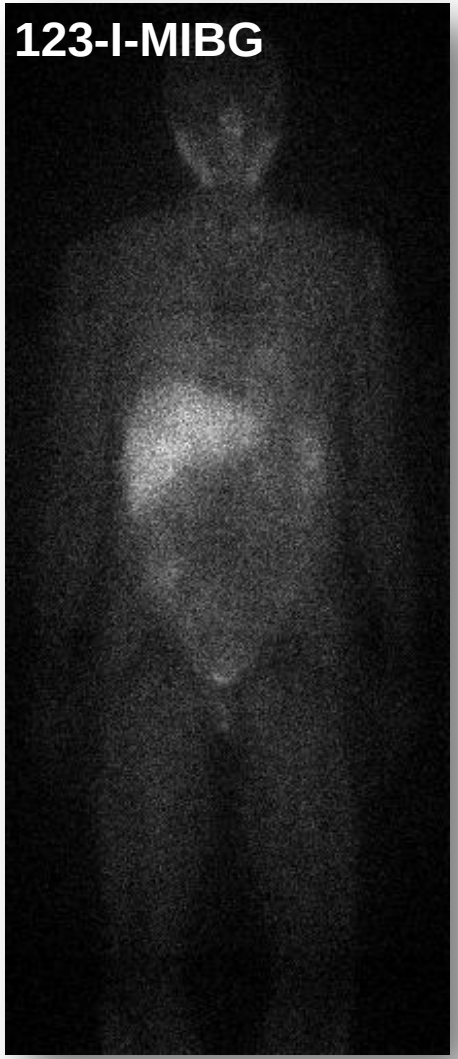




Same patient, same time frame

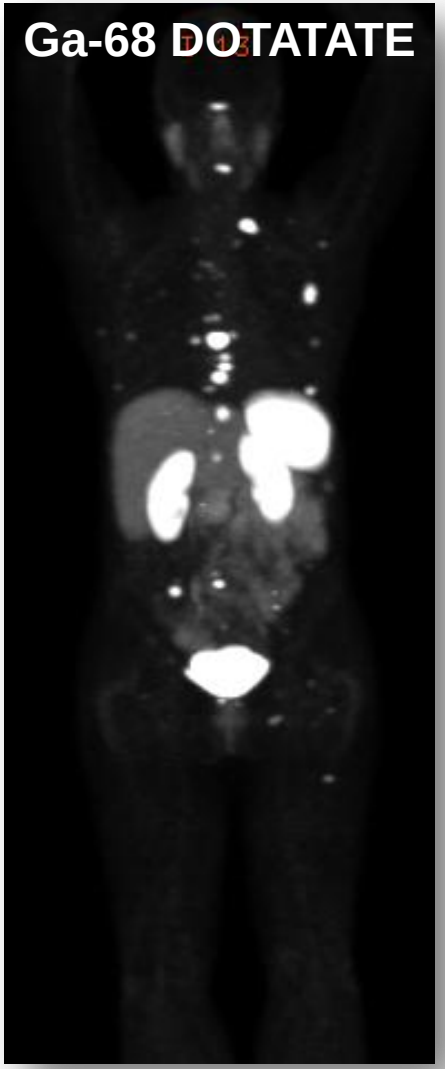
Although specific, 123-I-MIBG lacks sensitivity





Same patient, same time frame

Another example of superiority of Ga-68 DOTATATE PET over 123-I-MIBG



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**

Treatment (1)

- ✓ Combined α- and β-adrenergic blockade is one approach to control BP & prevent intraop hypertensive crises
- ✓ We start α-adrenergic blockade with phenoxybenzamine or 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.

Treatment (1)

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

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

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We block asymptomatic, normotensive patients too

We block biochemically silent pheochromocytomas too

If HR is <80 bpm 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 add a CCB to the doxazosin

Postop F/U (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.

Long-Term Postop F/U (2)

- 24-h urine fx cats & mets or plasma fx 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.

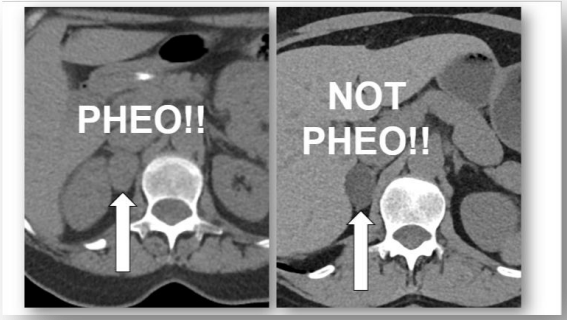
PPGL Take Home Points:

Medications That May ↑ Measured Levels of Norepinephrine and Normetanephrine

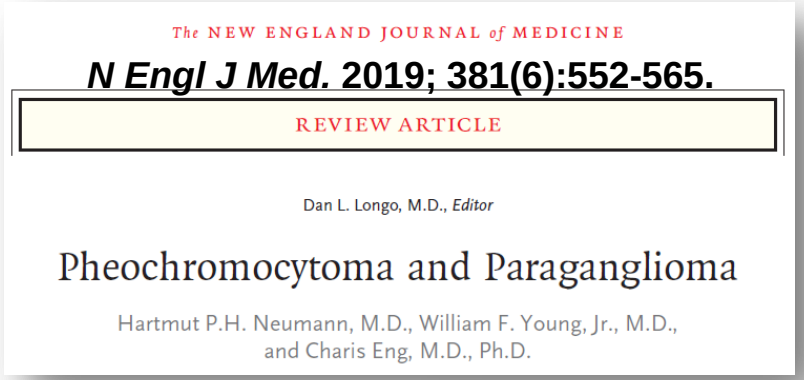
- ✓ Tricyclic antidepressants (including cyclobenzaprine)—2-10 X
- ✓ Levodopa—DA (10-20 X) & NE & Normet—2-4 X
- ✓ Drugs containing adrenergic receptor agonists (e.g., decongestants)—<2 X
- ✓ Amphetamines—variable
- ✓ Buspirone and antipsychotics—3-10 X
- ✓ SNRIs—50%-4 X
- ✓ SSRI—<50%
- ✓ Prochlorperazine—variable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

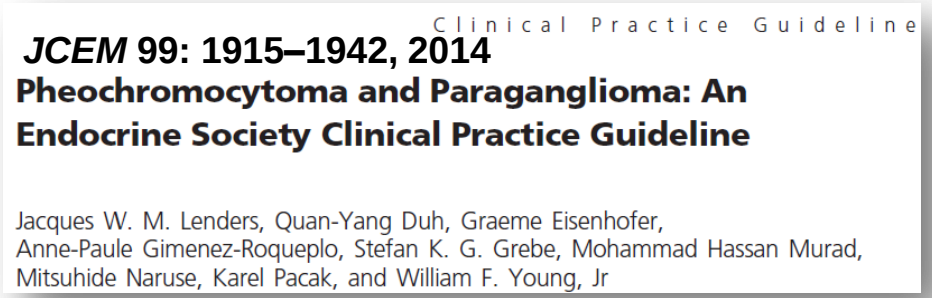
NOTE: With current assay methodology (tandem mass spec, HPLC), antihypertensive meds and acetaminophen DO NOT interfere with testing!

- ✓ They are rare
- ✓ Most + case detection tests are false + **nor**metanephrine—know the interfering drugs
- ✓ Most of the patients you see for pheochromocytoma will present with adrenal incidentaloma
- ✓ Adrenal incidentaloma→rely on imaging phenotype
- ✓ MRI is over-rated
- ✓ 40% of patients have a germline pathogenic variant that informs screening for other tumors & family testing
- ✓ Get nuclear imaging if looking for additional PGLs or mets

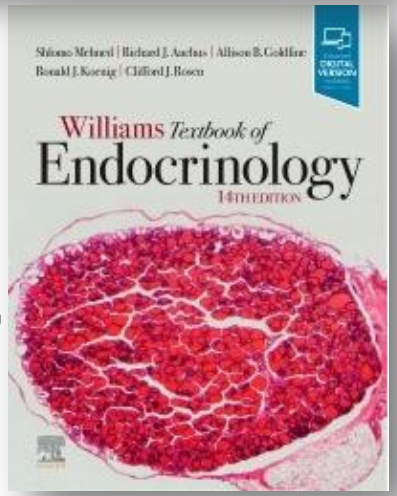


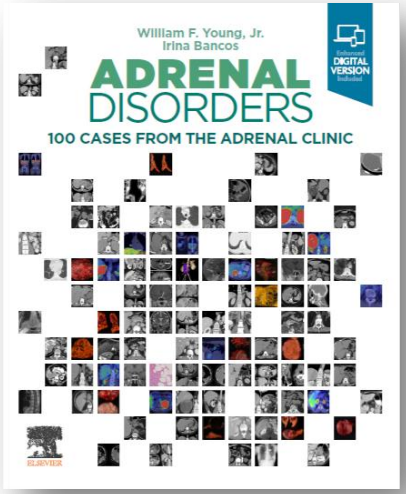
Background Reading





Endocrine Hypertension. In: Williams Textbook of Endocrinology, 14th Edition. 2020, Chap 16





Adrenal Disorders: 100 Cases from the Adrenal Clinic, 1st Edition. Released on Amazon April-2022

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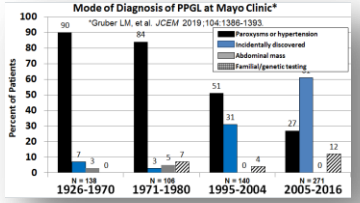
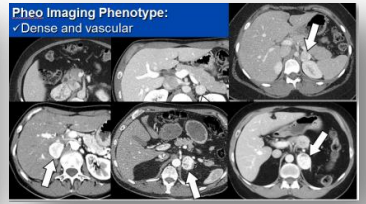
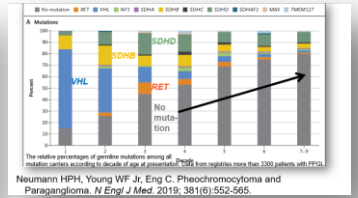
Update on Pheochromocytoma and Paraganglioma







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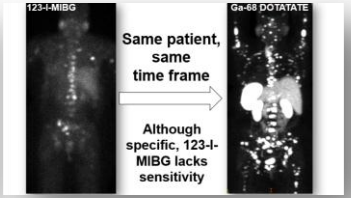

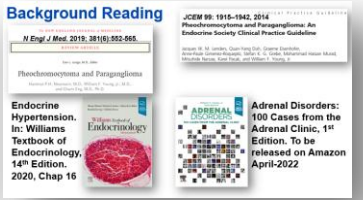

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Mayo Clinic, Rochester, MN USA

Day 2 – 28th August – 2:00 – 2:45 PM