MAYO CLINIC

ENDOCRINE INCIDENTALOMAS

WHAT TO DO WHEN YOU FIND ONE (AND YOU WILL!)

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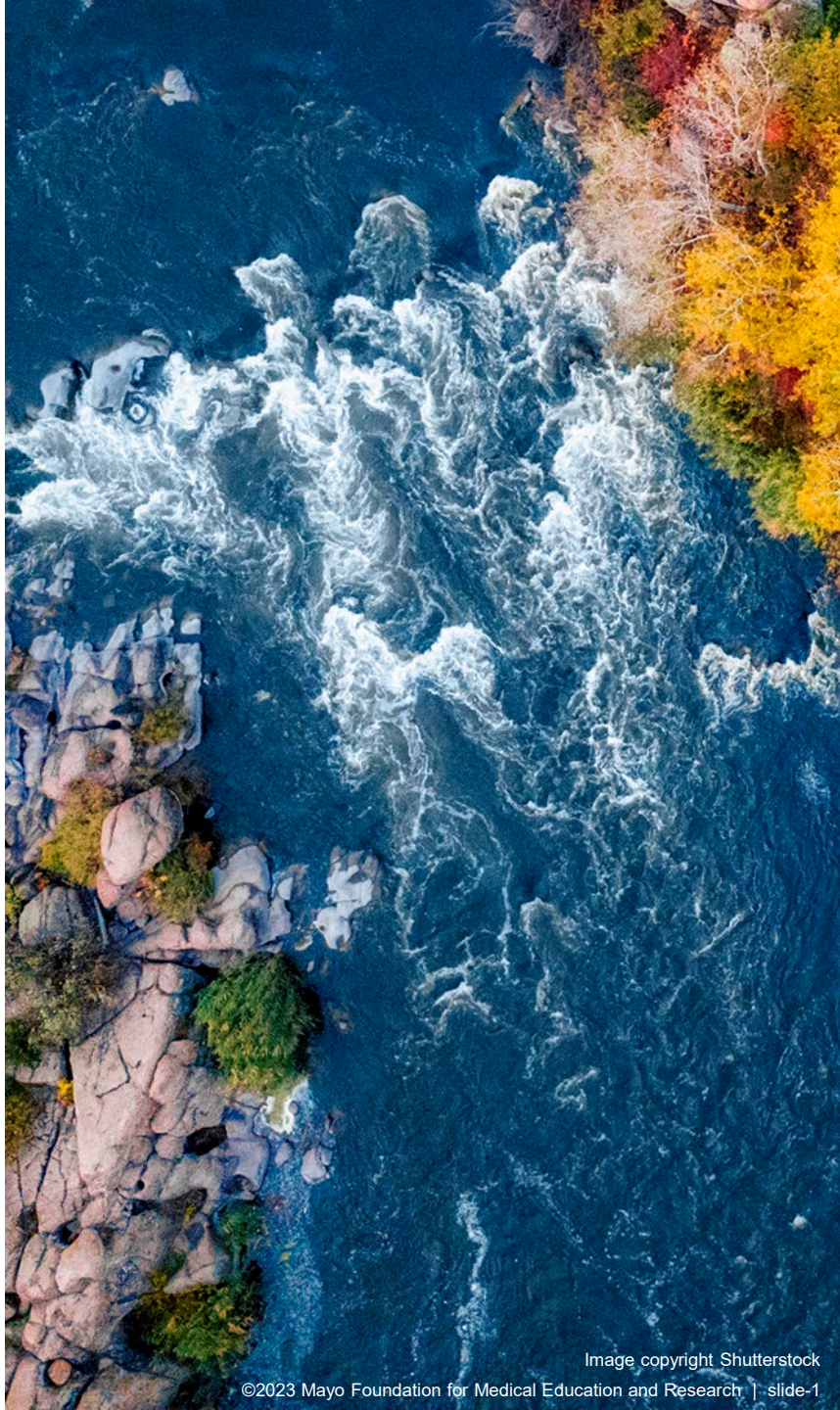

DISCLOSURES

- No financial disclosures
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LEARNING OBJECTIVES

At the conclusion of this session, participants should be able to:

- Describe common clinical features of endocrine incidentalomas including thyroid nodules, adrenal nodules, and pituitary masses
- Create an initial diagnostic plan for endocrine incidentalomas based on patient-specific factors
- Differentiate malignant and/or hormonal hypersecretion masses from benign endocrine incidentalomas
- Design an initial treatment plan for patients with endocrine incidentalomas
- Determine when referral to endocrinology is warranted

AUDIENCE POLL #1: I HAVE ENCOUNTERED THE FOLLOWING INCIDENTALOMA(S) IN PRACTICE

(SELECT ALL THAT APPLY)

A. Thyroid nodules

B. Adrenal nodules

C. Pituitary masses

D. Never! (Or should I say, not yet?)

AUDIENCE POLL #2: I AM COMFORTABLE ASSESSING & MANAGING THE FOLLOWING

(SELECT ALL THAT APPLY)

A. Thyroid nodules

B. Adrenal nodules

C. Pituitary masses

D. None, but I am eager to learn (that's why I'm here early on a Saturday morning)

THYROID NODULES

CASE #1

- Daniel H is a 38-year-old male who comes in for assessment after an MRI of the cervical spine completed for neck pain noted a possible 16 mm thyroid nodule on the right lobe
- Denies dysphagia, dysphonia, and dyspnea
- History of hypothyroidism on levothyroxine 100 mcg daily, last TSH 3 months ago was 1.4 mIU/L (0.3-4.2 mIU/L)
- His mother-in-law has a 4 cm thyroid nodule that has required a biopsy therefore he is wondering if he will need the same

THYROID NODULES

- Thyroid incidentalomas: Generally non-palpable thyroid nodules found on ultrasound or other imaging performed for various reasons
- Common (incidence varies – 19-72%)
- Majority are benign
- Why do we care?
  - Exclude malignancy (4-6.5% of thyroid nodules)
    - If we do, what is the follow-up?
  - Exclude hyperfunction (“Hot nodule(s)” → hyperthyroidism)

Data from:

Dean, D & Gharib, H. Epidemiology of Thyroid Nodules (2008). *Best Pract Res Clin Endocrinol Metab* 22(6):901-11
UpToDate, Diagnostic Approach to and Treatment of Thyroid Nodules, Accessed January 2023

THYROID MALIGNANCY

- Papillary (95%) > Follicular > Hurthle > Medullary > Anaplastic

- Generally, not warranted to w/u nodules < 1 cm for malignancy
  - Except: suspicious appearing or lymphadenopathy present

- Pearl/FYI
  - Post-thyroidectomy cancer patients may need suppressed TSH levels → talk to endocrine before adjusting levothyroxine

Data from: ATA 2015 Thyroid Nodule Guidelines Thyroid. 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020

THYROID NODULES
CLINICAL PRESENTATION

- Most asymptomatic
- Possible thyroid nodule on examination (4-7%)
  - Palpable vs non-palpable = same risk of malignancy
- Possible compressive symptoms → dysphonia, dysphagia, dyspnea
- Indicators of higher possibility of malignancy
  - History of head and/or neck irradiation
  - Total body irradiation for bone marrow transplant
  - Familial disorder associated with thyroid cancer (e.g., MEN-2)
  - Rapidly enlarging neck mass
  - Found on PET scan (?)

Data from: ATA 2015 Thyroid Nodule Guidelines Thyroid. 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020
UpToDate, Diagnosis of Thyroid Nodules (Accessed January 2023)

THYROID NODULES
WORK-UP

- Always get a TSH first
  - TSH low → ***refer***, will need radioactive iodine uptake (+/- thyroid ultrasound)
  - TSH normal (most patients) or high → **Thyroid ultrasound**
    - *TSH high – incidental finding, not related to nodule

Data from: ATA 2015 Thyroid Nodule Guidelines Thyroid. 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020
UpToDate, Diagnosis of Thyroid Nodules (Accessed January 2023)

THYROID ULTRASOUND

- Look at thyroid gland, nodule(s), and cervical lymph nodes
- Ultrasound features**
  - Features being considered: shape, echogenicity, calcifications, etc
    - Suspicious features?
    - Likelihood of malignancy?
  - TI-RADS score by ACR
    - Guides biopsy threshold
    - https://tiradscalculator.com

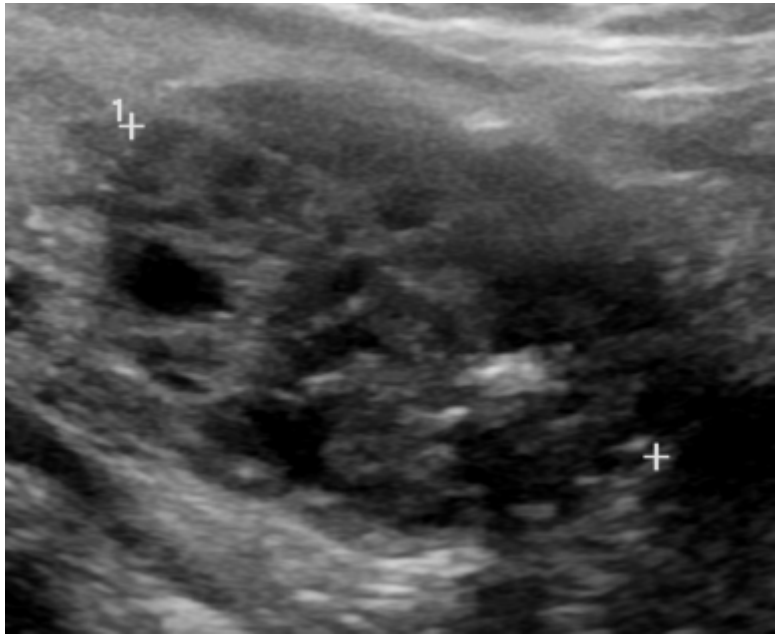
Data from:
UpToDate, Diagnosis of Thyroid Nodules (Accessed January 2023)
ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. http://tiradscalculator.com/wp-content/uploads/2017/05/JACR-TIRADS-2017-White-Paper.pdf

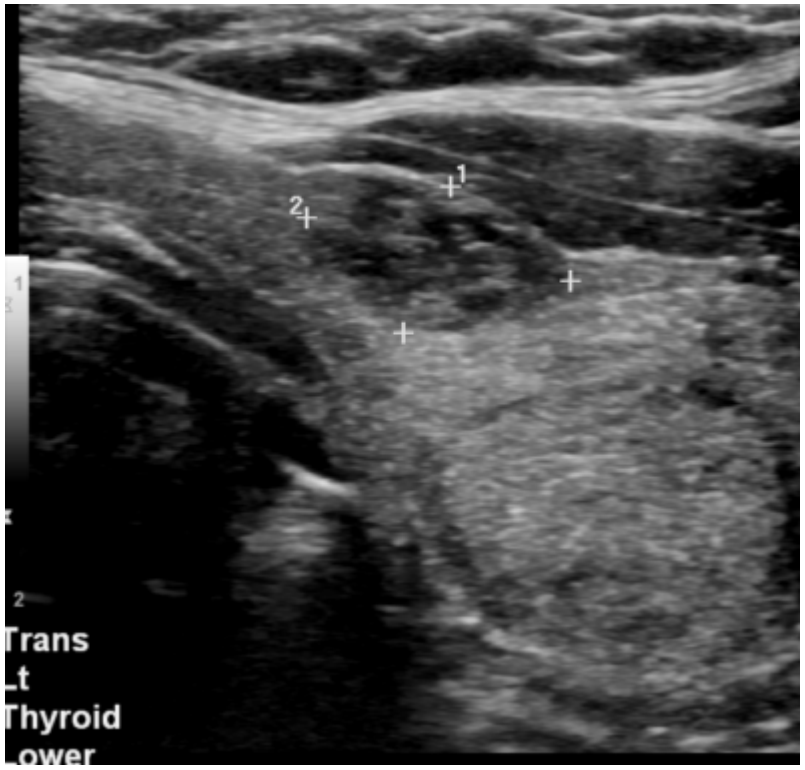
THYROID ULTRASOUND
SONOGRAPHIC FEATURES

Features Associated with Increased Risk of Malignancy	*Features Associated with Lower Risk of Malignancy*
• Hypoechogenicity • Solid composition • Microcalcifications • Irregular margins • Taller-than-wide shape • Suspicious lymphadenopathy	• Isoechoic or hyperechoic • Spongiform appearance • Simple cysts • Comet-tail artifact within cystic nodule • Uninterrupted eggshell classification

Personally Adapted from UpToDate: Diagnosis of Thyroid Nodules (Accessed January 2023)

THYROID NODULE PICTURES





THYROID ULTRASOUND
ACR TIRADS CLASSIFICATION & FNA GUIDANCE

- Composition (0-2 points)
- Echogenicity (0-3 points)
- Shape (0-3 points)
- Margin (0-3 points)
- Echogenic foci (0-3 points)

	Suspicion	*Points*	*Malignancy Risk*	*Biopsy Threshold*
TR1	Benign	0	0.3%	No biopsy
TR2	Not suspicious	2	1.5%	No biopsy
TR3	Mildly suspicious	3	4.8%	25 mm
TR4	Moderately suspicious	4-6	9.1%	15 mm
TR5	Highly suspicious	≥ 7	35%	10 mm

Personally Adapted from UpToDate: Diagnosis of Thyroid Nodules (Accessed January 2023) and ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. http://tiradscalculator.com/wp-content/uploads/2017/05/JACR-TIRADS-2017-White-Paper.pdf

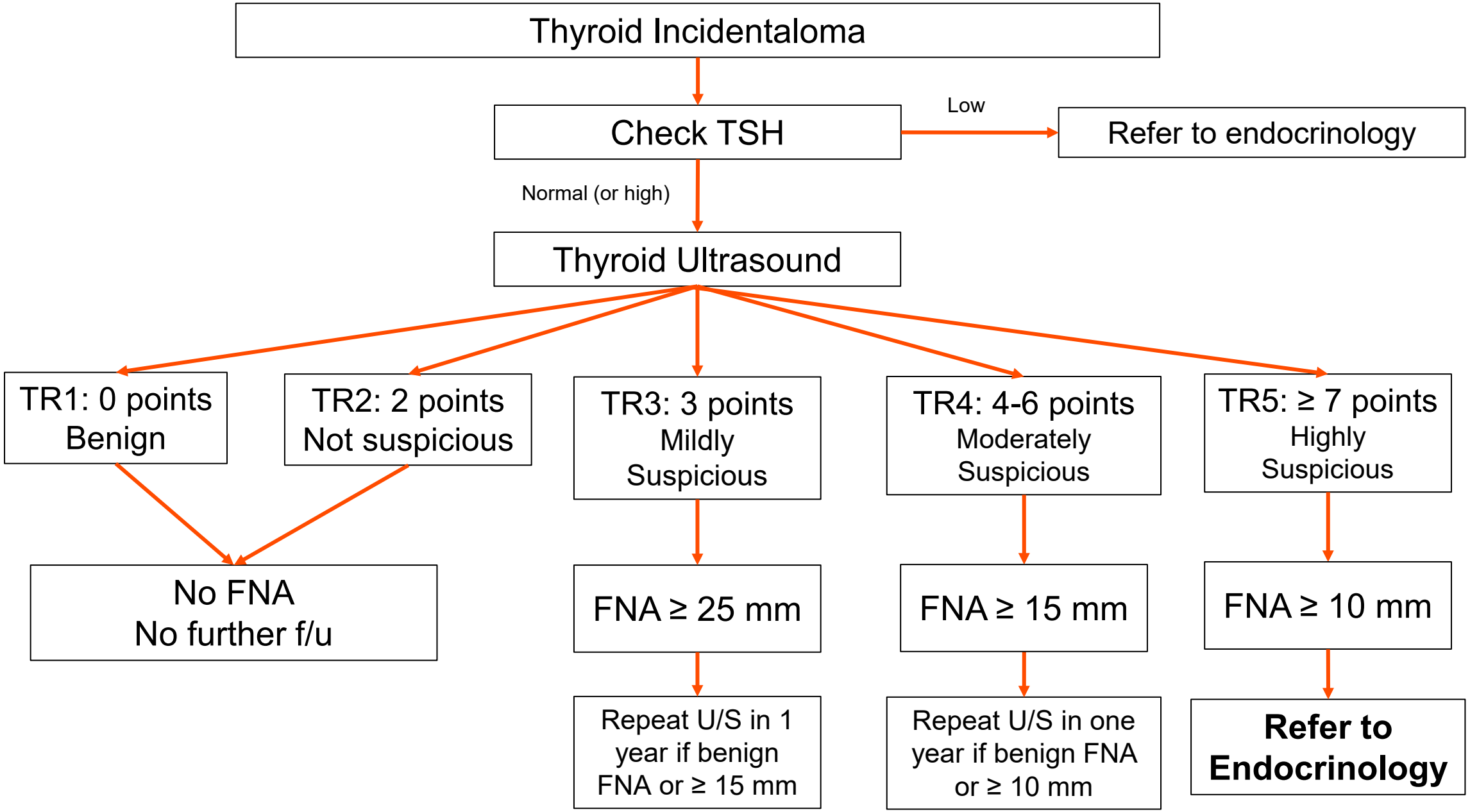
THYROID NODULES
FOLLOW-UP/TREATMENT

- FNA helps determine treatment
  - Suspicious for or malignant: *Refer for thyroidectomy*
  - Benign or not required: *Follow-up* ultrasound per guidelines

* Abnormal lymph nodes = increased risk of malignancy, refer

	Suspicion	*Ultrasound F/U*	*U/S Frequency**
TR1	Benign	None	n/a
TR2	Not suspicious	None	n/a
TR3	Mildly suspicious	≥ 15 mm	1, 3 and 5 years
TR4	Moderately suspicious	≥ 10 mm	1, 2, 3, and 5 years
TR5	Highly suspicious	≥ 5 mm	Yearly x 5 years

Personally Adapted from UpToDate: Diagnosis of Thyroid Nodules (Accessed January 2023) and ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. http://tiradscalculator.com/wp-content/uploads/2017/05/JACR-TIRADS-2017-White-Paper.pdf



Created by Justine Herndon, PA-C

THE REFERRAL

- Not all thyroid nodules require referral, but OK to refer all ≥ 10 mm if access to endocrinology is available
  - Primary care can f/u ultrasounds per guidelines where applicable
- Recommended referrals regardless:
  - Compressive symptoms
  - Low TSH with nodule(s)
  - Nodule meeting criteria for biopsy
  - Nodules with suspicious lymphadenopathy
  - Biopsy results indicate thyroid cancer
  - Family or personal history of thyroid cancer
  - Rapid enlarging thyroid mass → urgent → call

ADRENAL NODULES

CASE #2

- Chuck M is a 59-year-old male who read his ER visit records (2 days ago was seen for abdominal pain) and is concerned about an adrenal mass that he wasn’t aware of
- CT abdomen with contrast reported as “1.5 cm right adrenal mass, indeterminate but likely benign”
- PMHx: HTN (sub-optimally controlled on 3 agents), HLD, DM2 on insulin and metformin

ADRENAL INCIDENTALOMA

- High prevalence, 5-7% (up to 10% in older patients)
- 4 million/year discovered, often incidentally (*adrenal incidentaloma*)
- Why do we care?
  - Exclude malignancy (10-15%)
    - If we do, what is the follow-up?
  - Exclude hyperfunction (up to 50%)
    - Cortisol excess (MACS, Cushing's)
    - Aldosterone excess (primary hyperaldosteronism)
    - Catecholamine excess (pheochromocytoma)

Data from:

UpToDate; Evaluation and management of the adrenal incidentaloma; Retrieved May 2022
Bancos I & Prete A (2021). Approach to the Patient With Adrenal Incidentaloma. *J Clin Endocrinol Metab* 106(11):3331-3353
Elhassen et. al, Guidelines on management of adrenal incidentalomas. *Eur J Endocrinol*. 2016 Aug;175(2):G1-G34

ADRENAL INCIDENTALOMA
CLINICAL PRESENTATION

- Most are asymptomatic
- Cortisol excess
  - *If present, most often *mild autonomous cortisol secretion* (MACS)
    - Comorbidities of excess cortisol: obesity HTN, HLD, DM, bone density loss
  - Less likely full symptoms Cushing's
- Hyperaldosteronism
  - Difficult to control hypertension
  - Hypokalemia (< 40%)
- Pheochromocytoma
  - May be found incidentally and don't have typical symptoms!
  - "Classic triad" (˜40%): Headache, sweating, tachycardia
  - Paroxysmal HTN

Data from:
UpToDate; Evaluation and management of the adrenal incidentaloma; Retrieved May 2022
UpToDate; Clinical presentation and diagnosis of pheochromocytoma; Retrieved May 2022
Bancos I & Prete A (2021). Approach to the Patient With Adrenal Incidentaloma. *J Clin Endocrinol Metab* 106(11):3331-3353

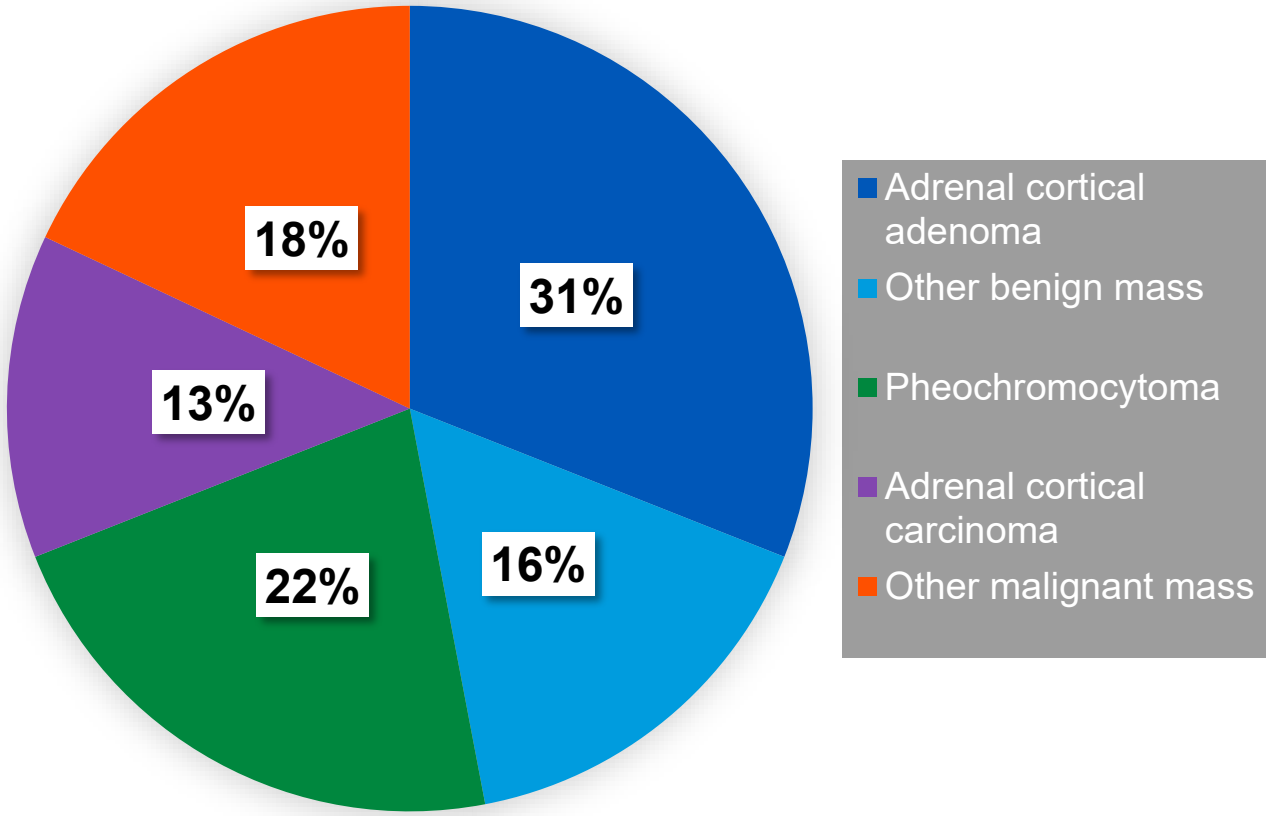
FACTORS ASSOCIATED WITH INCREASED RISK OF MALIGNANCY

- Younger age
- Bilateral masses
- History of malignancy
- Higher Hounsfield units (HU) on unenhanced CT scan
- More growth over a shorter period
- Size of mass

Data from:
Bancos I & Prete A (2021). Approach to the Patient With Adrenal Incidentaloma. *J Clin Endocrinol Metab* 106(11):3331-3353
UpToDate; Evaluation and management of the adrenal incidentaloma; Retrieved May 2022

ADRENAL INCIDENTALOMA
CLINICAL PRESENTATION

- Size
  - > 4 cm may be concerning for malignancy
  - Many are still benign (1/3)
  - *Refer*



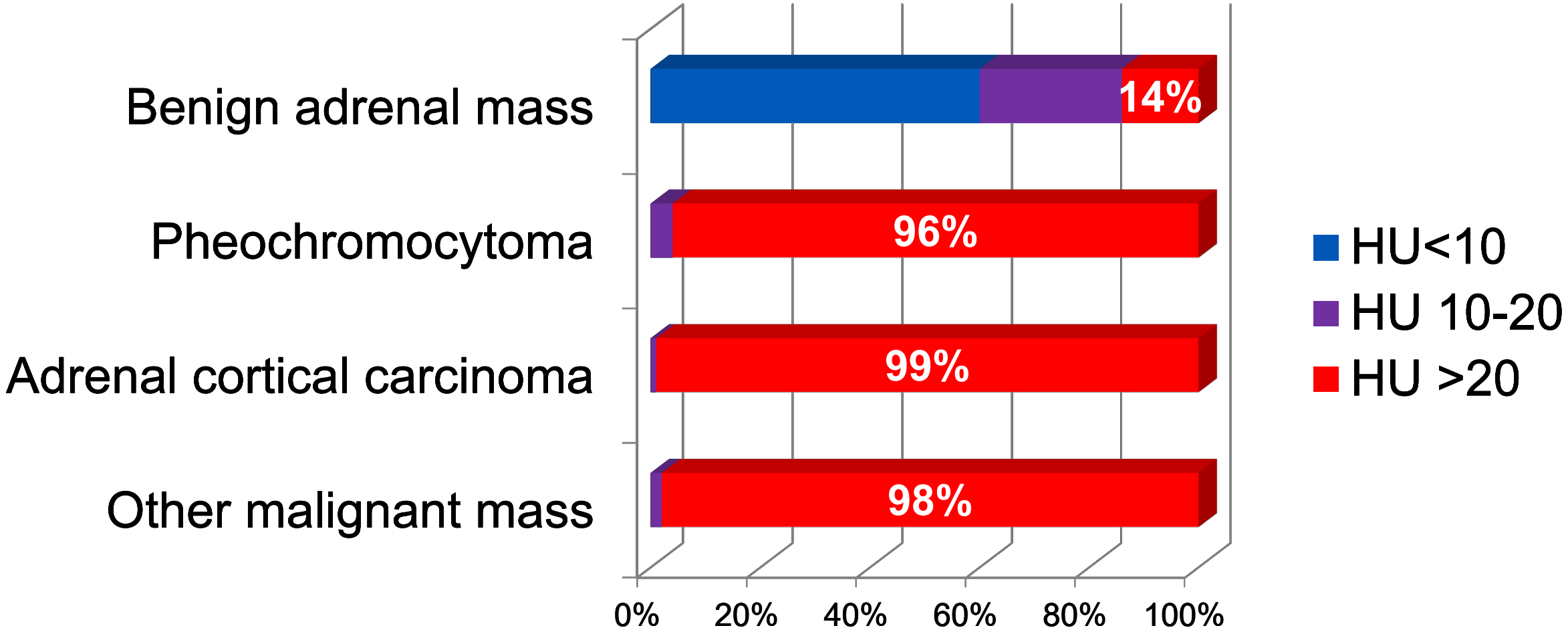
Data from Mantero et all, 2000, Iniguez et al, 2017, Mayo Clinic adrenal database, Eurine ACT study.
Image courtesy of Dr. Irina Bancos, Used with Permission

ADRENAL INCIDENTALOMA
WORK-UP

- Question when reviewing CT scans: Was it with or without contrast?
- If not – and resources/cost aren't a concern – get a CT scan without contrast
  - Hounsfield units (HU) are very helpful in determining benign vs malignant
    - < 10 = benign (high sensitivity)
    - ≥ 10 = Indeterminate, cannot rule out pheochromocytoma/adrenocortical carcinoma (ACC)
  - HU can also impact functional work-up

Data from:
Elhassen et. al, Guidelines on management of adrenal incidentalomas. *Eur J Endocrinol*. 2016 Aug;175(2):G1-G34
Bancos I & Prete A (2021). Approach to the Patient With Adrenal Incidentaloma. *J Clin Endocrinol Metab* 106(11):3331-3353

DIAGNOSTIC PERFORMANCE OF UNENHANCED CT TO DIAGNOSE ADRENAL MALIGNANCY (CUTOFF OF HU >10)



Courtesy of Dr. Irina Bancos, used with permission

ADRENAL INCIDENTALOMA
WORK-UP

- **All patients: 1-mg dexamethasone suppression test (DST)**
  - Rule out MACS
  - Normal cortisol < 1.8 mcg/dL
    - "Gray zone": 1.9-5.0 mcg/dL
    - Abnormal: > 5.0 mcg/dL
- **All patients with HTN: Renin, aldosterone, BMP/CMP**
  - Rule out hyperaldosteronism
  - Possible when elevated aldosterone + ***suppressed*** renin
    - Suspect when aldosterone is ≥ 10 AND plasma renin activity < 1
    - Often, aldosterone: renin ratio (ARR; Aldosterone ÷ renin) is > 20
- **HU ≥ 10 [indeterminate imaging]: 24-hour urine or plasma metanephrines**
  - Rule out pheochromocytoma

Data from:
Bancos I & Prete A (2021). Approach to the Patient With Adrenal Incidentaloma. *J Clin Endocrinol Metab* 106(11):3331-3353
Elhassen et. al, Guidelines on management of adrenal incidentalomas. *Eur J Endocrinol*. 2016 Aug;175(2):G1-G34

ADRENAL INCIDENTALOMA
PITFALLS IN TESTING

- Unable to get non-contrast CT? → test for all hormone hypersecretion syndromes
- 1-mg DST
  - Absorption of dexamethasone
  - Women on OCP's: ↑ cortisol, hard to interpret
- Renin/aldosterone
  - Mineralocorticoid receptor antagonists may impact results
- Pheochromocytoma evaluation
  - 11% false positive rate on plasma test
  - 24-hour urine → elevated results, may not be diagnostic

Data from :
Bancos I & Prete A (2021). Approach to the Patient With Adrenal Incidentaloma. *J Clin Endocrinol Metab* 106(11):3331-3353
Qureshi et al, (2017) The influence of the route of oestrogen administration on serum levels of cortisol-binding globulin and total cortisol. *Clin Endocrinol (Oxf)*, 66(5):632-5

ADRENAL INCIDENTALOMA
FOLLOW-UP/TREATMENT

- Most do not require treatment
- Surgery indications
  - Functional
  - Large and/or concerning for malignancy
- Re-Testing
  - 1-mg DST can be considered vs yearly x 4 years
- Re-Imaging
  - Benign: No re-imaging vs repeat in 12 months
  - Indeterminate: Re-image in 3-12 months; *consider referral*

Data from:
UpToDate; Evaluation and management of the adrenal incidentaloma; Retrieved May 2022
Bancos I & Prete A (2021). Approach to the Patient With Adrenal Incidentaloma. *J Clin Endocrinol Metab* 106(11):3331-3353
Elhassen et. al, Guidelines on management of adrenal incidentalomas. *Eur J Endocrinol*. 2016 Aug;175(2):G1-G34

THE ELUSIVE PHEOCHROMOCYTOMA

- Pheochromocytoma is uncommon
  - Most found are incidentally, asymptomatic
- Most patients with “spells” DO NOT have a pheochromocytoma
  - (or carcinoid, or another rare neuroendocrine tumor…)
  - Masses are usually LARGE when causing symptoms and easily found on imaging
- Medications that can affect testing (taper 2 weeks prior if needed)
  - TCAs, levodopa, decongestants, amphetamines, buspirone, most psychoactive agents, prochlorperazine, ethanol, reserpine

Data from: UpToDate: Diagnosis of Pheochromocytoma (Retrieved January 2023)

THE REFERRAL

- Reasonable to refer all adrenal masses if access is available
- Adrenal incidentalomas if not comfortable with work-up
- Indeterminate masses
- Masses ≥ 4 cm
- Suspected/confirmed
  - Hyperfunctioning adrenal mass
  - ACC → urgent referral → Call endocrinology

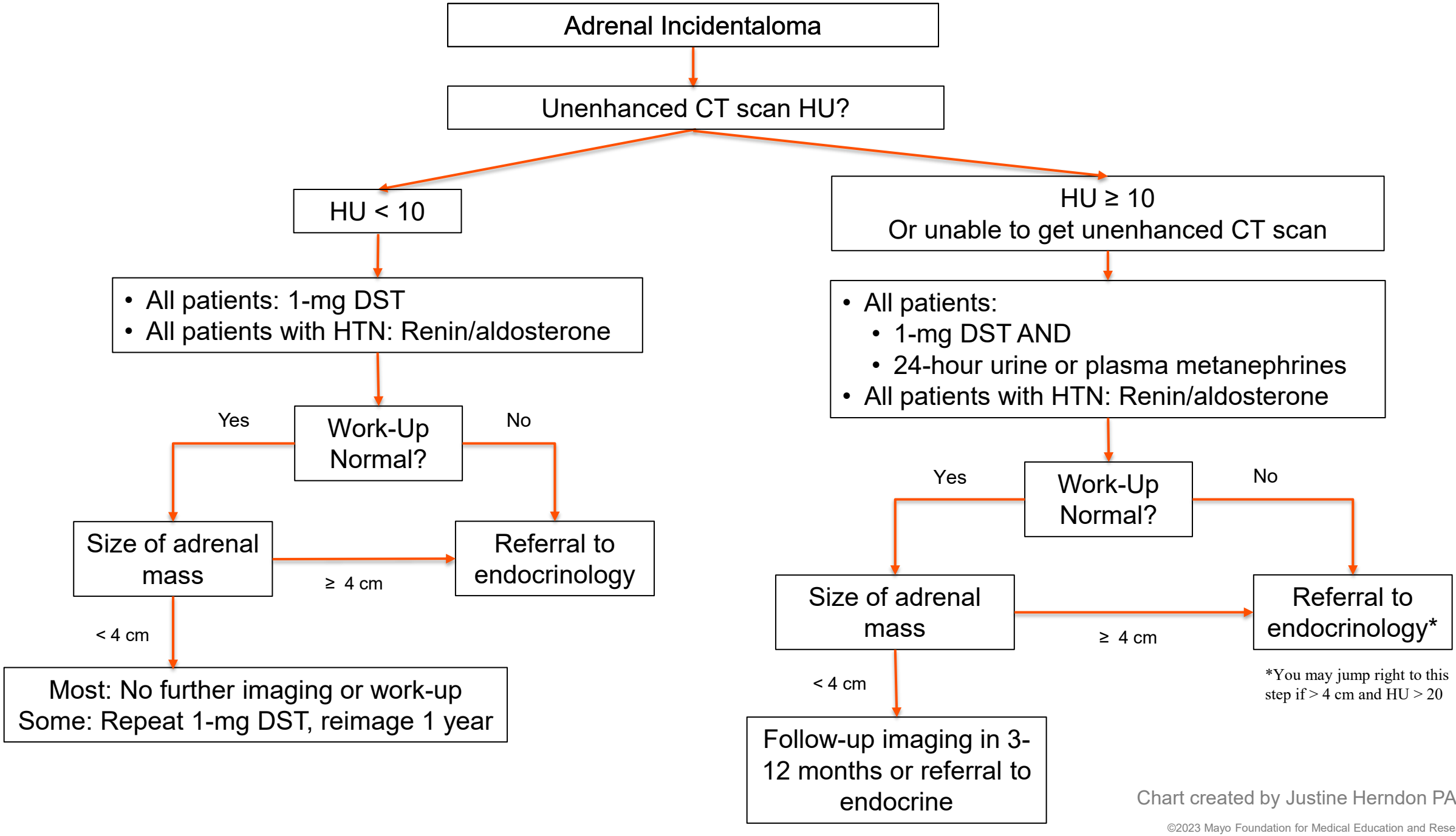


Chart created by Justine Herndon PA-C

PITUITARY MASSES

CASE #3

- Brianna G is a 35-year-old female who presents for an assessment of a 7 mm pituitary mass found incidentally when she had an MRI done for assessment of persistent tinnitus
- Outside of the tinnitus, she feels well, and she does not have any other symptom concerns
- She is concerned that this pituitary mass may be a cancer

CASE #3

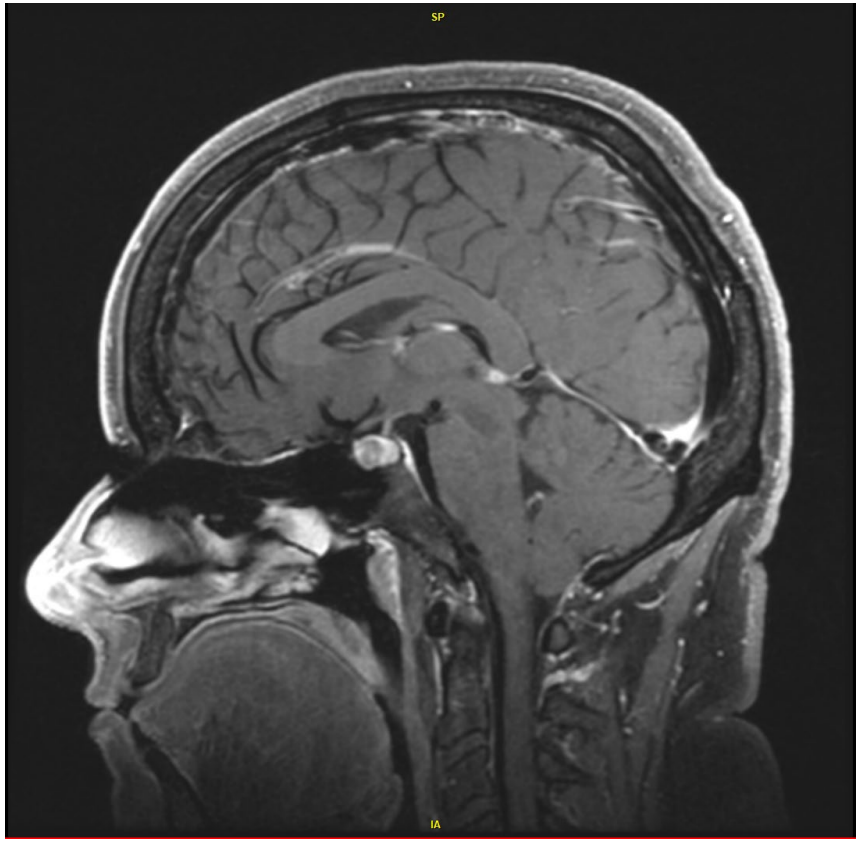


Photo on left not actual patient – used with permission

PITUITARY MASSES/ADENOMAS

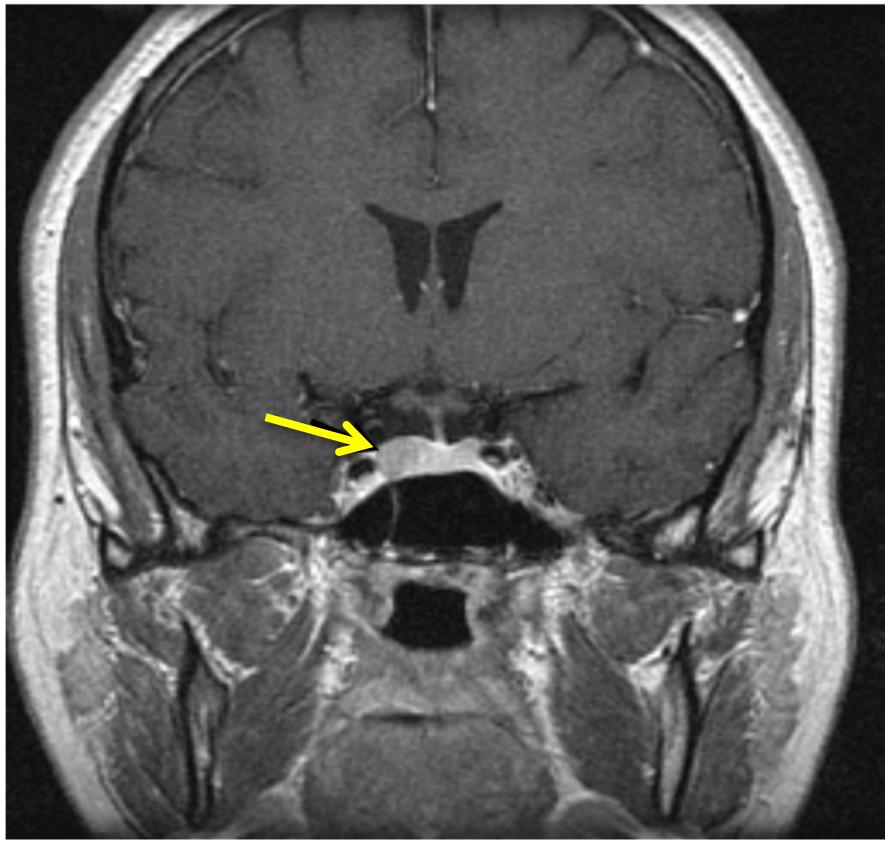
- Common, 10% of intracranial neoplasms
  - Most found incidentally (*pituitary incidentaloma*)
  - Otherwise discovered due to pituitary function changes and/or visual field compromise
- Why do we care?
  - Exclude compression/mass effect (optic chiasm)
  - Exclude hormonal hyperfunction
    - All require screening even if asymptomatic*
    - Prolactinoma > Acromegaly > Cushing syndrome > TSHoma
  - Exclude hormonal hypofunction in macroadenomas
  - Malignancy does not apply (< 1%)
  - What is the follow-up?

*Non-functioning tumors do exist (and are common), but best to rule out hyperfunction in all!

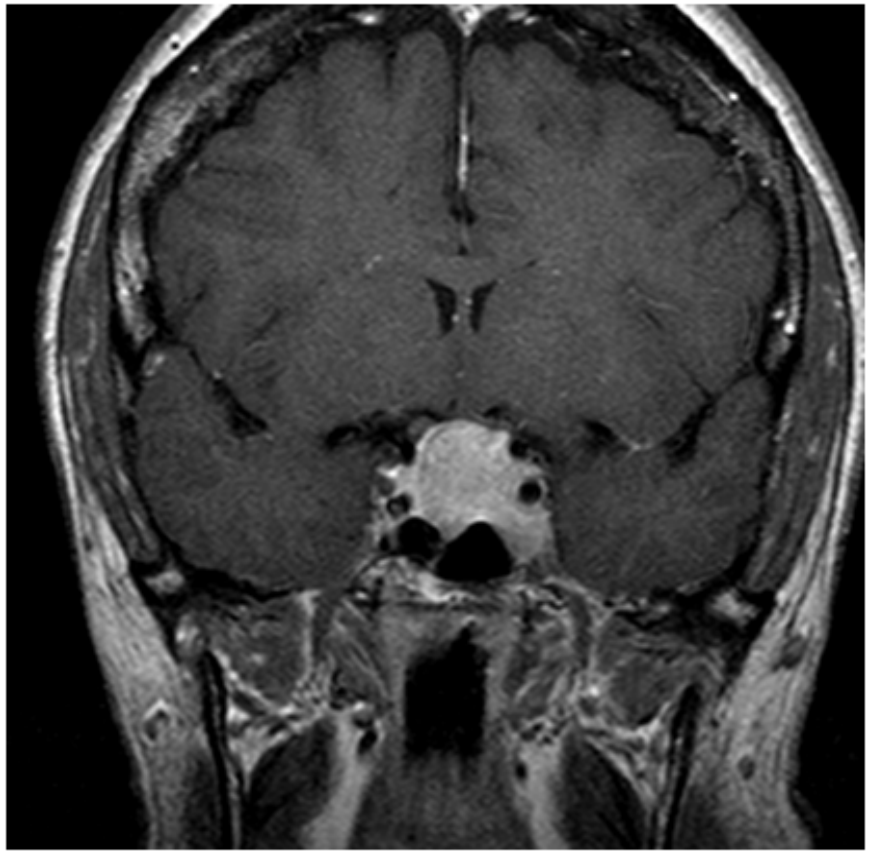
Data from:
UpToDate – Causes, presentation, and evaluation of sellar masses; Retrieved January 2023
Freda et al (2011): Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline, 96(4):894-904

PITUITARY ADENOMAS
CLASSIFICATION

- Microadenoma (< 10 mm)



- Macroadenoma (≥ 10 mm)



PITUITARY ADENOMAS
CLINICAL PRESENTATION

- Many asymptomatic
- Hyperfunction
  - PRL: Hypogonadism, galactorrhea
  - GH (acromegaly): Change in ring/shoe size, frontal bossing, large tongue
  - ACTH (Cushing's): Central adiposity, dark purple striae, extremity wasting/weakness
  - TSH (hyperthyroidism): Heat intolerance, palpitations, weight loss
- Hypofunction: Multiple non-specific symptoms (fatigue, weight change, N/V, etc)
- Headache????
- Possible peripheral vision loss in large tumors

Data from:
UpToDate – Causes, presentation, and evaluation of sellar masses; Retrieved January 2023
UpToDate – Clinical manifestations of hypopituitarism; Retrieved January 2023
Freda et al (2011): Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline, 96(4):894-904

PITUITARY ADENOMAS – WORK-UP
MICROADENOMAS

- Get a pituitary dedicated MRI if not already done
- Screening for hyperfunction
  - ***All patients should be screened with PRL and IGF-1***
  - Testing for Cushing's, TSHoma only if clinically suspected
- Screening for hypofunction
  - None vs consider for adenomas 6-9 mm in size

Data from:
UpToDate – Causes, presentation, and evaluation of sellar masses; Retrieved January 2023
UpToDate – Clinical manifestations of hypopituitarism; Retrieved January 2023
Freda et al (2011): Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline, 96(4):894-904

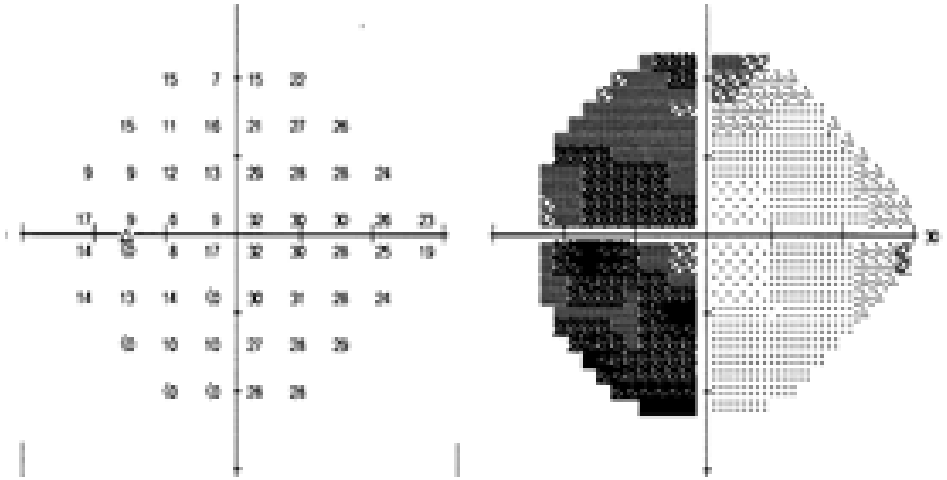
PITUITARY ADENOMAS – WORK-UP
MACROADENOMAS

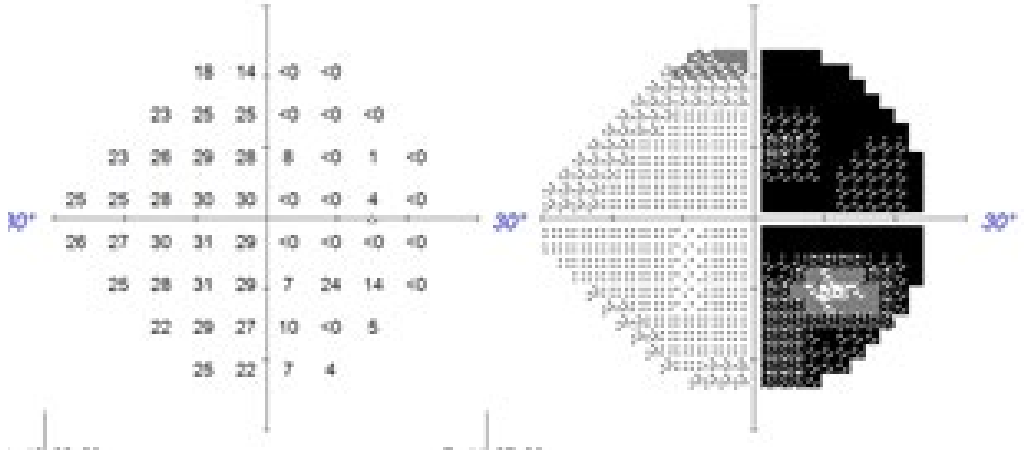
- Touching/near optic chiasm? → Visual field testing
  - Concern for bitemporal hemianopsia

- Screen for HYPER- and HYPO-function in all
  - PRL, IGF-1, Cortisol, Free T4 (*end organ function*)
  - Total + Bioavailable or Free Testosterone in men
  - Menstrual cycle assessment in premenopausal women

Data from:
UpToDate – Causes, presentation, and evaluation of sellar masses; Retrieved January 2023
UpToDate – Clinical manifestations of hypopituitarism; Retrieved January 2023
Freda et al (2011): Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline, 96(4):894-904

PITUITARY ADENOMAS – WORK-UP
VISUAL FIELDS





PITUITARY ADENOMAS
FOLLOW-UP/TREATMENT

- Most will be referred to endocrinology
- Surgical resection
  - Functional adenomas (except prolactinomas)
  - Many non-functioning macroadenomas, esp. if visual field loss
- Re-imaging if no surgical resection
  - Microadenomas
    - 90% do not grow to a clinically significant size
    - < 5 mm: No further MRIs
    - 5-9 mm: MRI yearly x 2 years, decrease frequency thereafter
  - Macroadenomas
    - MRI at 6 months, then yearly
    - Repeat visual fields if touching/near optic chiasm

Data from:
UpToDate – Causes, presentation, and evaluation of sellar masses; Retrieved January 2023
UpToDate – Clinical manifestations of hypopituitarism; Retrieved January 2023
Freda et al (2011): Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline, 96(4):894-904

LESSONS FROM CASE 3

- Why do we need to work-up a pituitary mass with no symptoms?
  - Subclinical disease
  - Case #3 sent for surgical resection
    - Pathology: Staining for growth hormone and chromogranin
    - Still in remission 8 years later!

PITFALLS IN TESTING
"ABNORMALLY NORMAL" LABS

- Pituitary hormones can appear normal, but the end organ function is not → indicator of pituitary dysfunction
- Example:
  - Free T4 0.4 (low), TSH 2.3 mIU/L (normal)
  - TSH *should* be high with that low of a T4 in a normal functioning pituitary!
  - This has an impact on clinical monitoring!

CUSHING'S DISEASE/SYNDROME

- Endogenous Cushing's is **RARE**
  - Weight gain and "buffalo hump" don't always need work-up
  - What is your suspicion?
- Work-up
  - Screening cortisol not helpful
  - Better screening tests (1 or more depending on suspicion):
    - 1-mg dexamethasone suppression test
    - 24-hour urine cortisol
    - Midnight salivary cortisols
  - Once confirmed, get ACTH & send to endocrine
- True Cushing's disease may not have pituitary tumor seen on MRI (but it is there)
  - HOWEVER, don't image the patient until you have confirmed a diagnosis!

Data from: UpToDate, Establishing the Diagnosis of Cushing Syndrome (Accessed January 2023)

HYPOPITUITARISM PEARLS

- If you diagnose: Replace cortisol first
- Don’t use cortisol level to guide adrenal insufficiency treatment
- Follow free T4, not TSH, for these patients
- Menstrual cycle history more helpful than estrogen levels
- Rare if no history of surgery, radiation or trauma
  - If you diagnose, get a pituitary MRI

Data from:
UpToDate, Causes of Hypopituitarism; Retrieved January 2023
UpToDate; Clinical manifestations of hypopituitarism; Retrieved January 2023

THE REFERRAL

- Most pituitary adenomas should be referred to endocrine, if you have access
  - Microadenomas – functional
  - All macroadenomas
  - Post-op patients with recurrence
- If many years out of surgery – Ok for primary care to check labs yearly (e.g., IGF-1 if in remission from acromegaly)
- Hypopituitarism
- No need to refer patients to r/o Cushing's
  - Do initial work-up, if normal, most often no referral needed
  - If questions or abnormal- refer/call

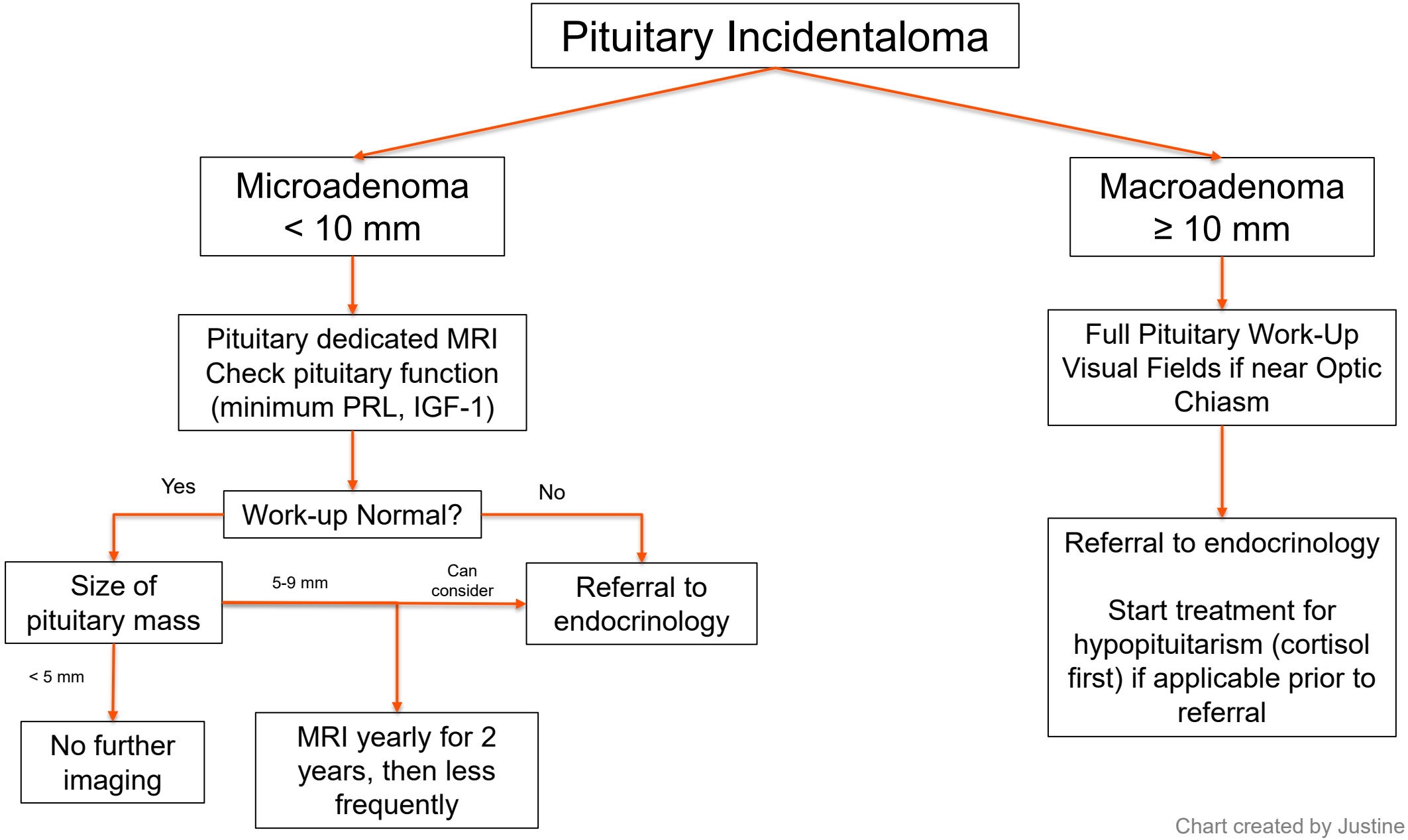


Chart created by Justine Herndon PA-C

MAYO CLINIC

QUESTIONS?

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THANK YOU

- Additional content expert input from: Dr. Irina Bancos, Dr. Neena Natt, Michele Merten APRN, CNP, DNP; All from Mayo Clinic Rochester, MN, Division of Endocrinology

