UNIVERSITÄTS KLINIKUM ulm

MEDICOVER NEUROENDOKRINOLOGIE

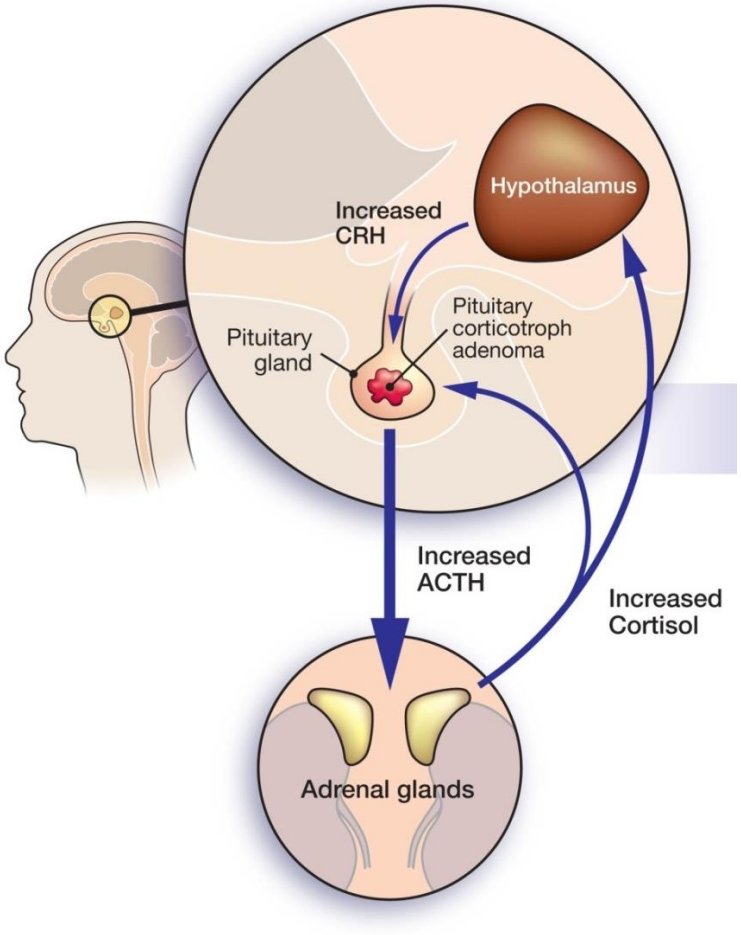
DIAGNOSTIC CHALLENGES IN CUSHING'S SYNDROME:
NAVIGATING COMPLEXITY IN ENDOCRINE PRACTICE

Dr. med. Kathrin H. Popp

ICEMU 21.-23. May 2025

Cushing's syndrome

- Rare disorder caused by prolonged exposure to glucocorticoid excess
- Prevalence of Cushing's disease about 5 cases per 100,000
- Most frequent: iatrogenic Cushing's syndrome due to long-term high-dose glucocorticoid therapy



Pathogenesis:

- ACTH-dependent: 65-70 %
  - **64 % ACTH-producing corticotrophic pituitary adenoma (Cushing's disease)**
  - 6 % ectopic
  - < 1% CRH-producing tumor
- ACTH-independent: 30 %
  - **22 % Adrenal Adenoma**
  - 1 % Adrenocortical carcinoma
  - 5 % Macronodular adrenal hyperplasia (PBMAH)
  - 2 % Primary pigmented nodular adrenocortical disease (PPNAD)
  - < 1% McCune-Albright Syndrome

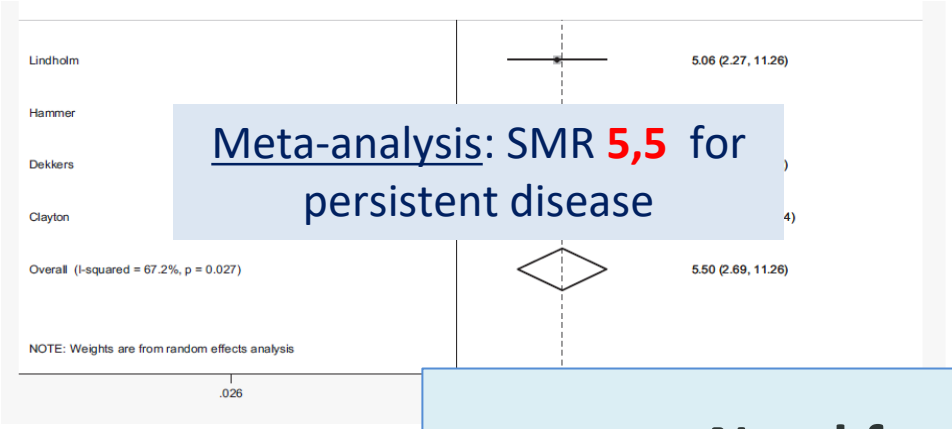
(ACTH-independent: Exogenous glucocorticoid use)

Agustsson et al., 2015; Sharma et al., 2015; Reincke, Fleseriu, JAMA, 2023

Cushing's syndrome - Mortality

Mortality and Morbidity in Cushing's Disease over 50 Years in Stoke-on-Trent, UK: Audit and Meta-Analysis of Literature

R. N. Clayton, D. Raskauskiene, R. C. Reulen, and P. W. Jones

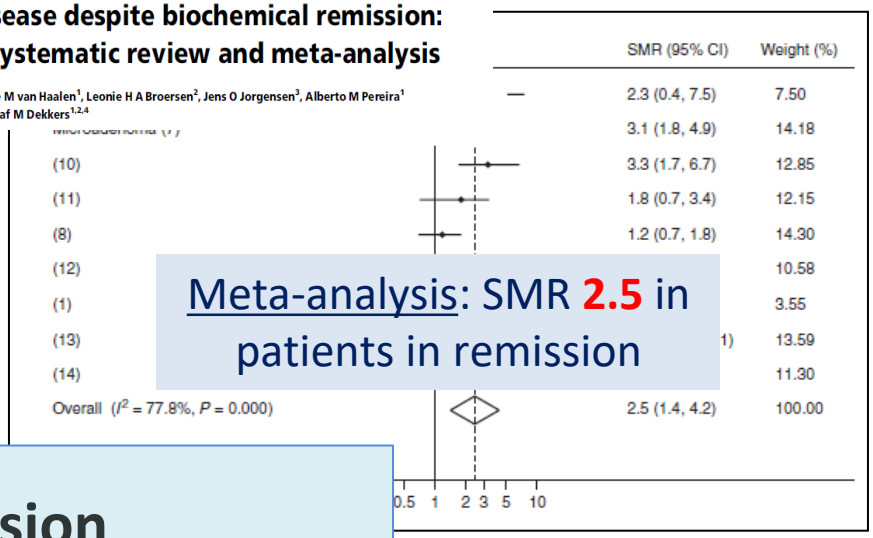


Meta-analysis: SMR **5,5** for persistent disease

MANAGEMENT OF ENDOCRINE DISEASE

Mortality remains increased in Cushing's disease despite biochemical remission: a systematic review and meta-analysis

Femke M van Haalen[1], Leonie H A Broersen[2], Jens O Jorgensen[3], Alberto M Pereira[1] and Olaf M Dekkers[1,2,4]



Meta-analysis: SMR **2.5** in patients in remission

Need for rapid remission

Overall and Disease-Specific Mortality in Patients With Cushing Disease: A Swedish Nationwide Study

Oskar Ragnarsson,[1,2] Daniel S. Olsson,[1,2] Eleni Papakokkinou,[1,2] Dimitrios Chantzichristos,[1,2] Per Dahlqvist,[3] Elin Segerstedt,[3] Tommy Olsson,[3] Maria Petersson,[4,5] Katarina Berinder,[4,5] Sophie Bensing,[4,5] Charlotte Höybye,[4,5] Britt Edén-Engström,[6] Pia Burman,[7] Lorenza Bonelli,[7] Cecilia Follin,[8] David Petranek,[8] Eva Marie Erfurth,[8] Jeanette Wahlberg,[9] Bertil Ekman,[9] Anna-Karin Åkerman,[10] Erik Schwarcz,[10] Ing-Liss Bryngelsson,[11] and Gudmundur Johannsson[1,2]

J Clin Endocrinol Metab, June 2019, 104(6):2375–2384

			% CI)
All			
In remission (n = 419)	89	47.3	1.9 (1.5–2.3)
Not in remission (n = 40)	22	3.2	6.9 (4.3–10)
Remission status unknown (n = 43)	22	4.2	5.2 (3.3–7.9)
Women			
In remission (n = 325)			
Not in remission (n = 31			
Remission status unknov			
Men			
In remission (n = 94)			
Not in remission (n = 9)			
Remission status unknov			
Circulatory diseases			
In remission (n = 419)	42	16.5	2.5 (1.8–3.4)
Not in remission (n = 40)	10	1.1	9.5 (4.5–17)
Remission status unknown (n = 43)	11	1.3	8.2 (4.1–15)
Ischemic heart disease			
In remission (n = 419)	21	7.7	2.7 (1.7–4.2)
Not in remission (n = 40)	5	0.5	10.7 (3.5–25)
Remission status unknown (n = 43)	7	0.7	10.4 (4.2–22)
Malignant neoplasms			
In remission (n = 419)	15	15.9	0.9 (0.5–1.6)
Not in remission (n = 40)	2	0.9	2.0 (0.3–7.4)
Remission status unknown (n=43)	1	1.7	0.6 (0.02–3.3)

After remission, SMR remains elevated, especially for cardiovascular diseases, ischemic heart disease and malignancies

Clayton et al., JCEM, 2011; Van Haalen et al., EJE, 2015; Ragnarsson et al., JCEM, 2019

Cushing‘s-Syndrome - Whom to Screen?

Multiple Symptoms — OR: 18.0

Myopathy — OR: 6.0

Osteoporosis — OR: 3.8

Metabolic Syndrome — OR: 2.7

Adrenal Adenoma — OR: 2.4

Obesity — OR: 0.1

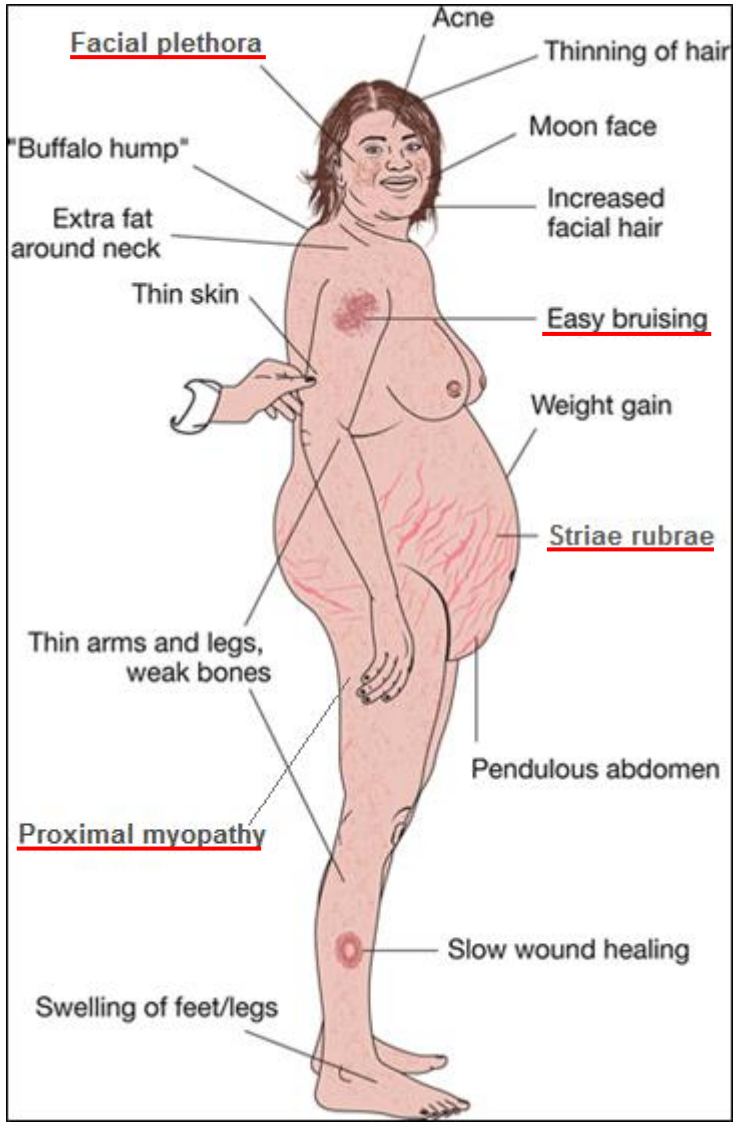
3.2 We recommend testing for Cushing’s syndrome in the following groups:

- Patients with unusual features for age (e.g. osteoporosis, hypertension)
- Patients with multiple and progressive features, particularly those who are more predictive of Cushing’s syndrome
- Children with decreasing height percentile and increasing weight
- Patients with adrenal incidentaloma compatible with adenoma.

Reasons for consultation	CS ruled out (N = 284)	CS (N = 93)	*P*	Odds ratio	CI
Obesity/weight gain	30%	4%	< .001	0.11	0.04-0.30
Incidentaloma	8%	17%	.01	2.4	1.2-4.7
Metabolic syndrome	4%	11%	.02	2.7	1.1-6.5
Osteoporosis	2%	8%	.02	3.8	1.1-12.9
Myopathy	2%	10%	< .001	6.0	2.0-18.3
Multiple symptoms[a]	1%	16%	< .001	18.0	5.1-63.8
Visual diagnosis (by external physician)[b]	5%	3%	.3		
Lab results[c]	4%	2%	.4		
Hypertension	12%	5%	.07		
Visual diagnosis (by patient)[d]	2%	1%	.2		
“PCOS” symptoms (acne, hirsutism, menstrual changes)	8%	6%	.7		
Fatigue/tiredness	5%	3%	.3		
Edema	4%	3%	.7		
Psychiatric disorders	3%	1%	.2		
Sweating	2%	1%	.4		
Clinical signs[d]	1%	2%	.6		
Other	5%	5%	≥ .999		

Nieman et al., JCEM, 2008; Braun et al., JCEM, 2022

Cushing‘s-Syndrome - signs and symptoms



SPECIAL FEATURE

Clinical Practice Guideline

The Diagnosis of Cushing’s Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, John Newell-Price, Martin O. Savage, Paul M. Stewart, and Victor M. Montori

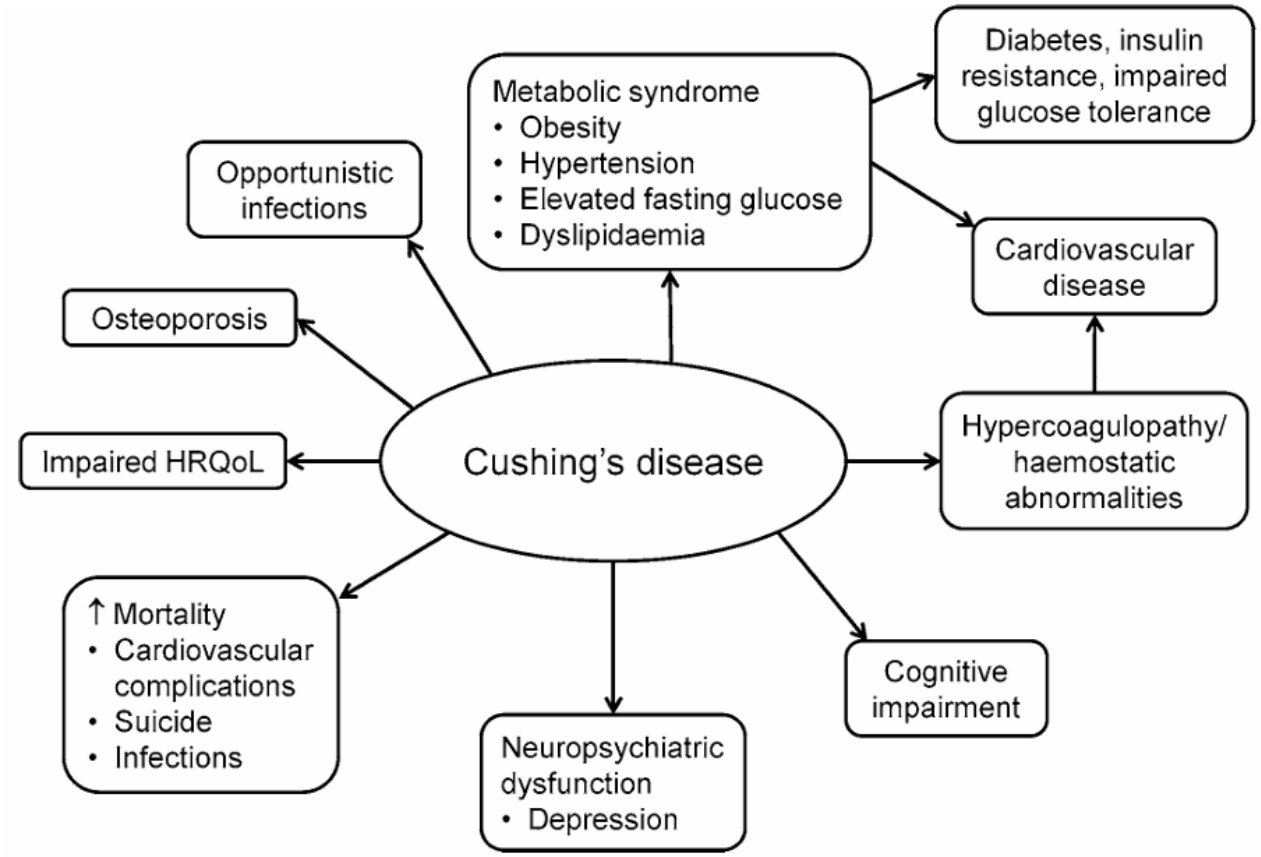
TABLE 1. Overlapping conditions and clinical features of Cushing’s syndrome[a]

Symptoms	Signs
Features that best discriminate Cushing’s syndrome; most do not have a high sensitivity	
	Easy bruising
	Facial plethora
	Proximal myopathy (or proximal muscle weakness)
	Striae (especially if reddish purple and > 1 cm wide)
	In children, weight gain with decreasing growth velocity
Cushing’s syndrome features in the general population that are common and/or less discriminatory	
Depression	Dorsocervical fat pad (“buffalo hump”)
Fatigue	Facial fullness
Weight gain	Obesity
Back pain	Supraclavicular fullness
Changes in appetite	Thin skin[b]
Decreased concentration	Peripheral edema
Decreased libido	Acne
Impaired memory (especially short term)	Hirsutism or female balding
Insomnia	Poor skin healing
Irritability	
Menstrual abnormalities	
In children, slow growth	In children, abnormal genital virilization
	In children, short stature
	In children, pseudoprecocious puberty or delayed puberty

Metabolic symptoms (e.g. diabetes mellitus 2, arterial hypertension) And osteoporosis

Nieman et al., 2008; Colao et al., 2014; Sharma et al., 2015

Cushing‘s-Syndrome - Comorbidities



Endocrine Society Clinical Guideline 2015: ***“Physicians should aggressively treat comorbidities and involve the appropriate specialists, including rehabilitation medicine”***

Pivonello et al., Endocrine, 2017

Cushing‘s-Syndrome - DD Hypercortisolism

- Physiologic hypercortisolism in the absence of Cushing’s syndrome
- „ Pseudo-Cushing’s“, may mimic clinical signs but is not due to autonomous cortisol production
- reversible after resolution of underlying cause (e.g., depression, alcoholism)

- Pregnancy
- Psychiatric disorders (especially **depression**, **alcoholism**)
- Metabolic diseases (**obesity**, poorly controlled Diabetes)
- Nutrition (malnutrition, anorexia nervosa)
- Physical stress (hospitalization, surgery, pain)
- Intense chronic exercise

Nieman et al., JCEM, 2008; Yorke et al., Int J Endocrinol. 2017

Cushing‘s-Syndrome - diagnostics

Indication for diagnostics:

- **Clinical suspicion**
- **Younger adults, age-inappropriate diseases**
- **All patients with adrenal cortical incidentaloma**

↓

Exclusion of exogenous glucocorticoid intake!

↓

Overnight 1 mg dexamethasone test (DST) (48h 2mg/d-Test)	**Late night salivary cortisol (≥2x)**	**24h-urinary free cortisol (UFC) (≥2x)**
Norm < 1,8 µg/dl (50 nmol/liter) *Sensitivity 80-95%, Specificity 80-95%*	**Norm** < 1,5 ng/ml (4,1 nmol/L) *Sensitivity 92-100%, Specificity 85-100%*	**Norm** 50-85 µg/24h, indeterminate 85-170 µg/24h, varies by laboratory/assay *Sensitivity 45-71%, Specificity -100%*
Cave		
Contraceptives,depression, anticonvulsants, anxiety disorder, Kidney failure	Age, Hypertension, Diabetes, oral hygiene, eating, tooth brushing, oral lesions	Sex, age, excretion, GFR, salt intake

↓

Inconspicuous:	**Conspicuous:**
→ **Cushing's syndrome unlikely or cyclic CS**	→ **Additional medical examination**

Fleseriu et al., The Lancet Diabetes & Endocrinology, 2021

Interference with Diagnostic tests

Overnight 1 mg Dexamethasone Suppression Test (DST)

- **Liver and Kidney Dysfunction**: Reduced dexamethasone metabolism (CYP3A4 liver) and reduced renal clearance → false negative
- Hypoalbuminämie: ↑free dexamethasone circulation → false negative
- **Stress/Depression/Anxiety Disorders**: „Pseudo-Cushing's" due to chronic HPA axis activation → false positive
- **Contraceptives:** increase transcortin/CBG → false positive
- **Rapid metabolizer/Z.n. bariatric surgery:** reduced dexamethason resorption → false positive
- Useful in shift-workers

Late-night Salivary Cortisol (LNSC)

- **Oral hygiene, eating, toothbrushing**: Blood contamination (due to minor gum bleeding) can falsely increase cortisol levels. → false positive
- **Stress, depression, sleep disorders, shift-work, smokeing**: May lead to falsely elevated values. → false positive
- **Age and metabolic conditions (hypertension, diabetes)**: May alter cortisol secretion patterns with increased baseline LNSC → false positive
- Lower specifity in adrenal CD

24-hour Urinary Free Cortisol (UFC)

- **Renal function (GFR impairment)**: Can lead to falsely low results due to reduced cortisol clearance. → false negative
- **Salt intake, hydration status, polydipsie (> 5l)**: Can influence cortisol excretion
- **Sex and age**: May influence cortisol metabolism

Nieman et al., JCEM, 2008

Cushing‘s-Syndrome - Drug-Interference

Increase CBG: Falsely elevate cortisol

- Estrogens
- Mitotane

→ false positives

Increase UFC results:

- Carbamazepine (increase)
- Fenofibrate (increase if measured by HPLC)
- Some synthetic glucocorticoids (immunoassays)
- Drugs that inhibit 11 Beta-Hydroxysteroid-Dehydrogenase (licorice, carbenoxolone)

→ false positives

Dexamethasone Suppression Test:

Induction of CYP 3A4: Accelerate dexamethasone metabolism

- Phenobarbital
- Phenytoin
- Carbamazepine
- Primidone
- Rifampicin
- Rifapentine
- Ethosuximide
- Pioglitazone

→ false positives

Inhibition of CYP 3A4: Impair dexamethasone metabolism

- Aprepitant/fosaprepitant
- Itraconazole
- Ritonavir
- Fluoxetine
- Diltiazem
- Cimetidine

→ false negative

Nieman et al., JCEM, 2008

Cushing‘s-Syndrome - diagnostics

Prefer Overnight 1 mg DST for:

- Depression
- Anxiety disorder
- Obesity
- Alcohol abuse
- Typ 2 Diabetes

Prefer following tests for special populations:

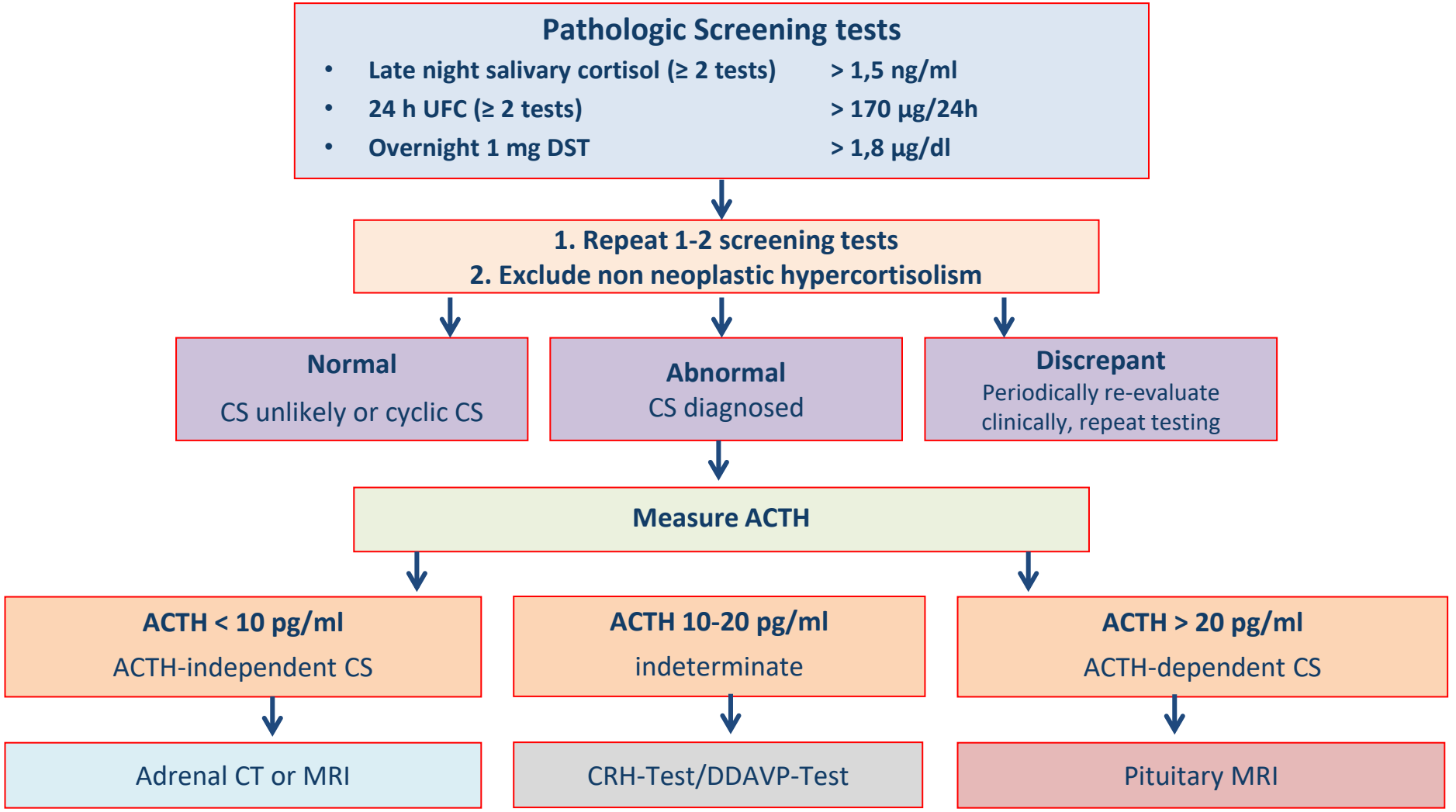
- **Pregnancy**: UFC
- **Epilepsy**: UFC, LNST
- **Kidney failure** GFR < 20 ml/min: 1-mg DST
- **Cyclic CS**: UFC, LNST
- **Adrenal incidentaloma**: 1-mg DST, LNST

Pregnancy:

- 2nd/3rd. Trimester: Cortisol 3-fold increased
- Preserved cortisol circadian rhythmic
- dexamethasone testing has an increased potential for false-positive

Nieman et al., Clinical Practice Guideline, 2008

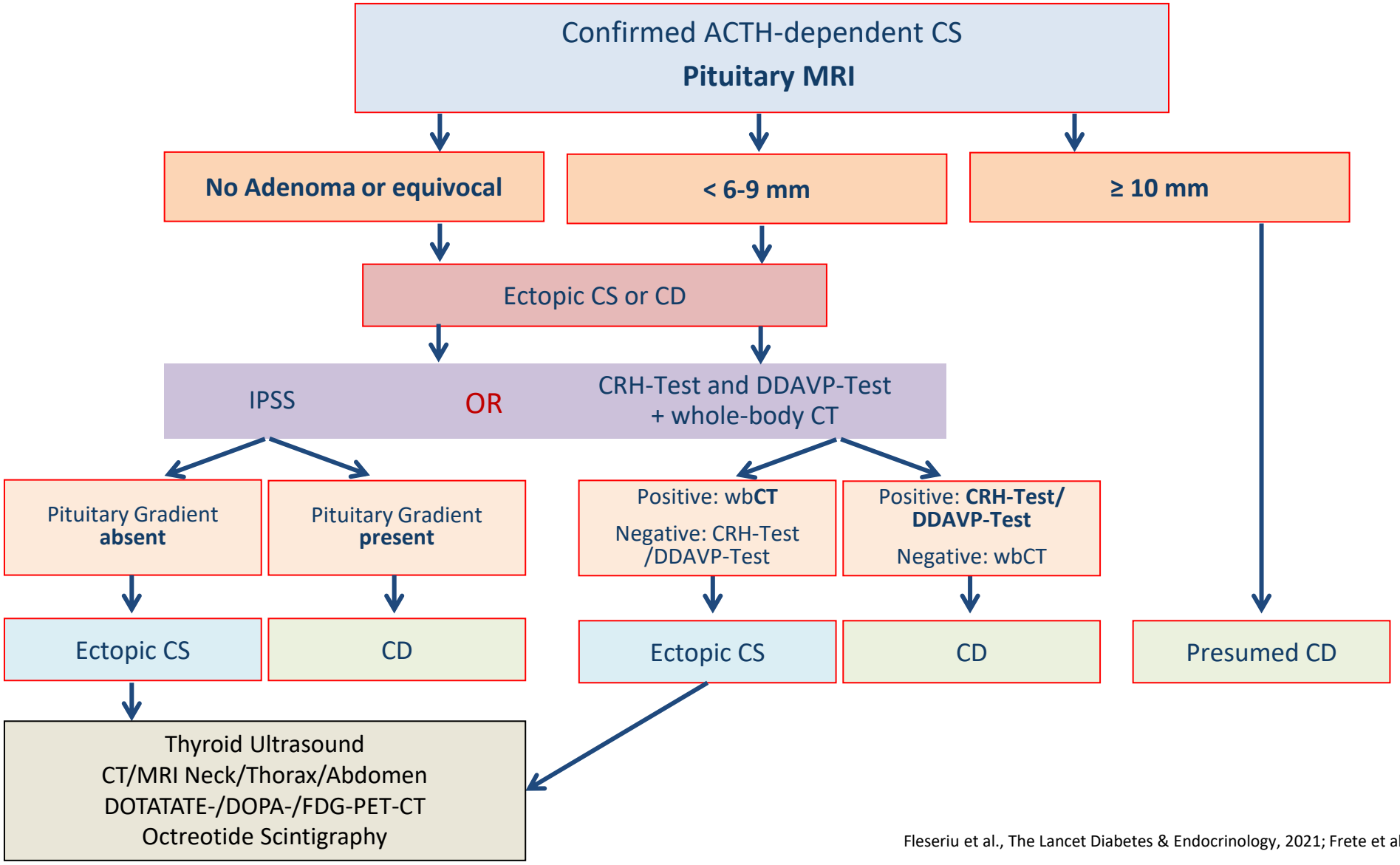
Cushing‘s-Syndrome - diagnostics



CAVE: CRH is currently not available in large parts of the world

Fleseriu et al., The Lancet Diabetes & Endocrinology, 2021

Cushing‘s-Syndrome - ACTH-dependent CS



Fleseriu et al., The Lancet Diabetes & Endocrinology, 2021; Frete et al., JCEM, 2020

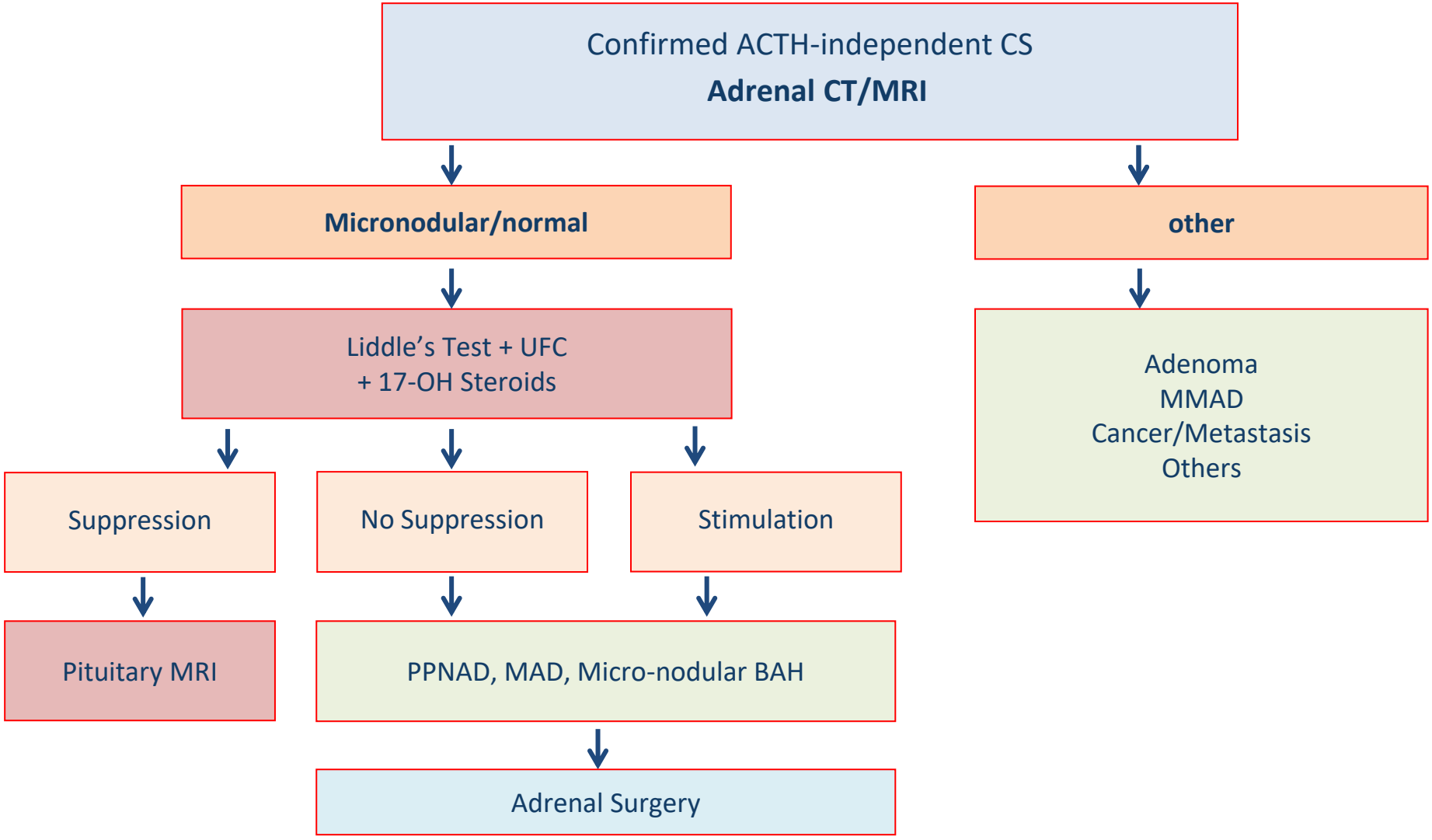
Cushing‘s-Syndrome - ACTH-dependent CS

Cushing's disease confirmed if:

MRI	**Adenoma ≥ 10 mm detection in 60% (CAVE: 10% incidentalomas!)**
High-dose Dexamethasonetest (8mg)	**Cortisol suppressed by >50% (CAVE: largely obsolete, false positives in some ectopic ACTH-producing tumors)**
CRH-test	**ACTH stimulated by >50%, cortisol by >20%**
DDAVP-Test	**ACTH stimulated by >33%, cortisol by >18%**
IPSS - Inferior petrosal sinus catheter	**ACTH gradient basal >2.0 after CRH >3.0** (should only be done in experienced centers)
Liddle-Test (16 mg DST)	**Cortisol (UFC/Serum) suppressed by < 50%**
CRH-Test+Liddle-Test	**Suppression of serum cortisol by >30 % in the 16 mg DST over 3 days and/or increased serum cortisol in CRH test >20 % differentiates pituitary from ectopic genesis, sensitivity and specificity of 95 %.**
Plasma steroid profile (+DST/CRH-test)	**↑Cortisol, ↑ ACTH, ↓11-deoxycortisol, ↑17-OHP and other steroid precursors (Ectopic: =/↑ 11-deoxycortisol)**

Fleseriu et al., The Lancet Diabetes & Endocrinology, 2021; Frete et al., JCEM, 2020

Cushing‘s-Syndrome - ACTH-independent CS



Pereira A, Dekkers O., The Piuitary, 2022

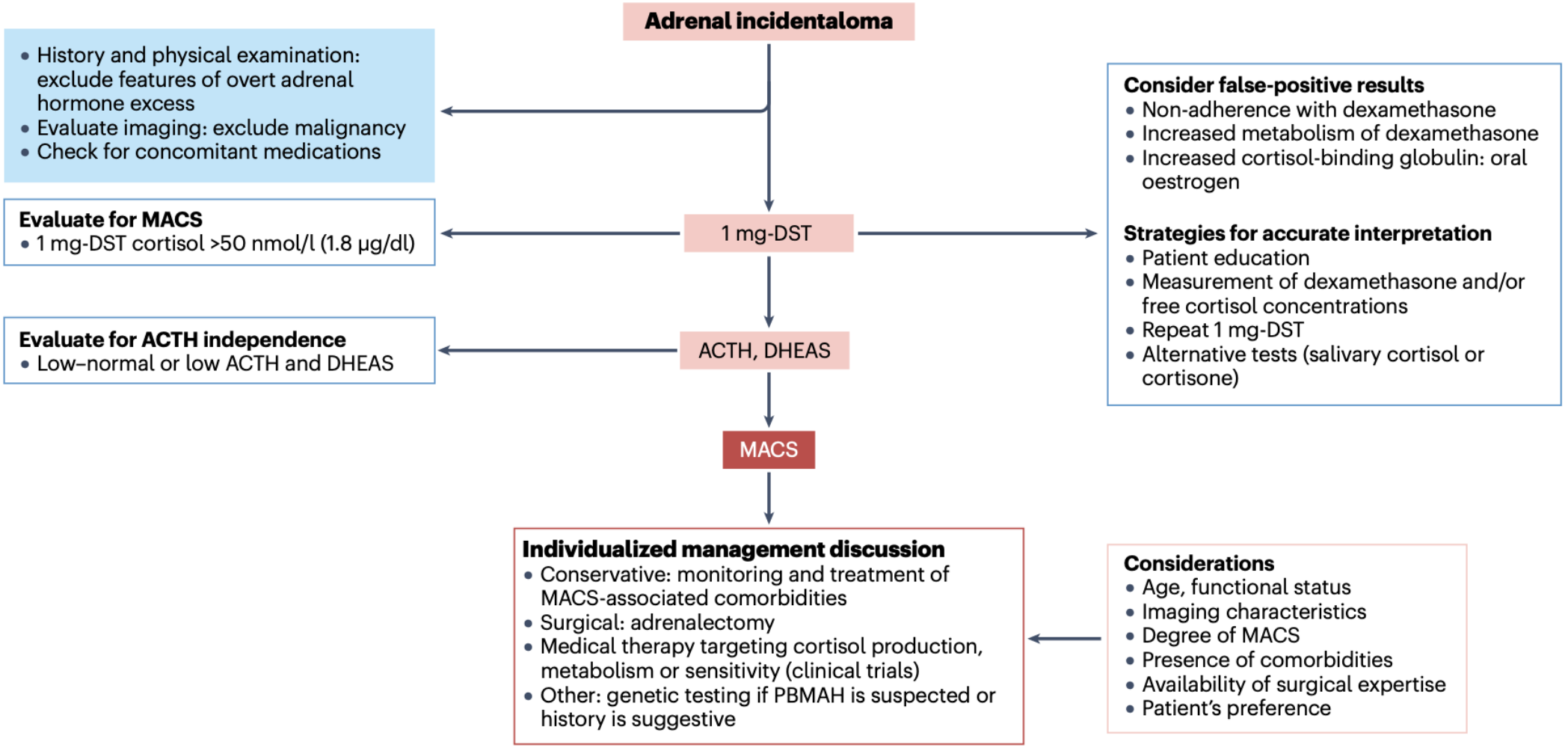
Cushing‘s-Syndrome - ACTH-independent CS

	Adrenal CS confirmed if:
CT Abdomen	non-adenoma-typical HU (>10 or ≥20) or size >4 cm
MRI	Delayed enhancement after gadolinium administration, signal enrichment
High-dose Dexamethasonetest (8mg)	**no Cortisol suppression**
Liddle-Test (16 mg DST)	no Cortisol suppression (UFC/Serum)
CRH-test	**ACTH < 30 pg/ml**
Selective adrenal venous sampling (AVS)	Lateralization Index (LI) ≥ 2 (or ≥ 3): unilateral adrenal CD Lateralization Index < 2: bilateral adrenal CD (likely BAH)
Plasma steroid profile (+DST/CRH-test)	↑Cortisol, ↓ ACTH, ↑11-deoxycortisol

Pereira A, Dekkers O., The Piuitary, 2022

Cushing‘s-Syndrome – Adrenal Adenoma

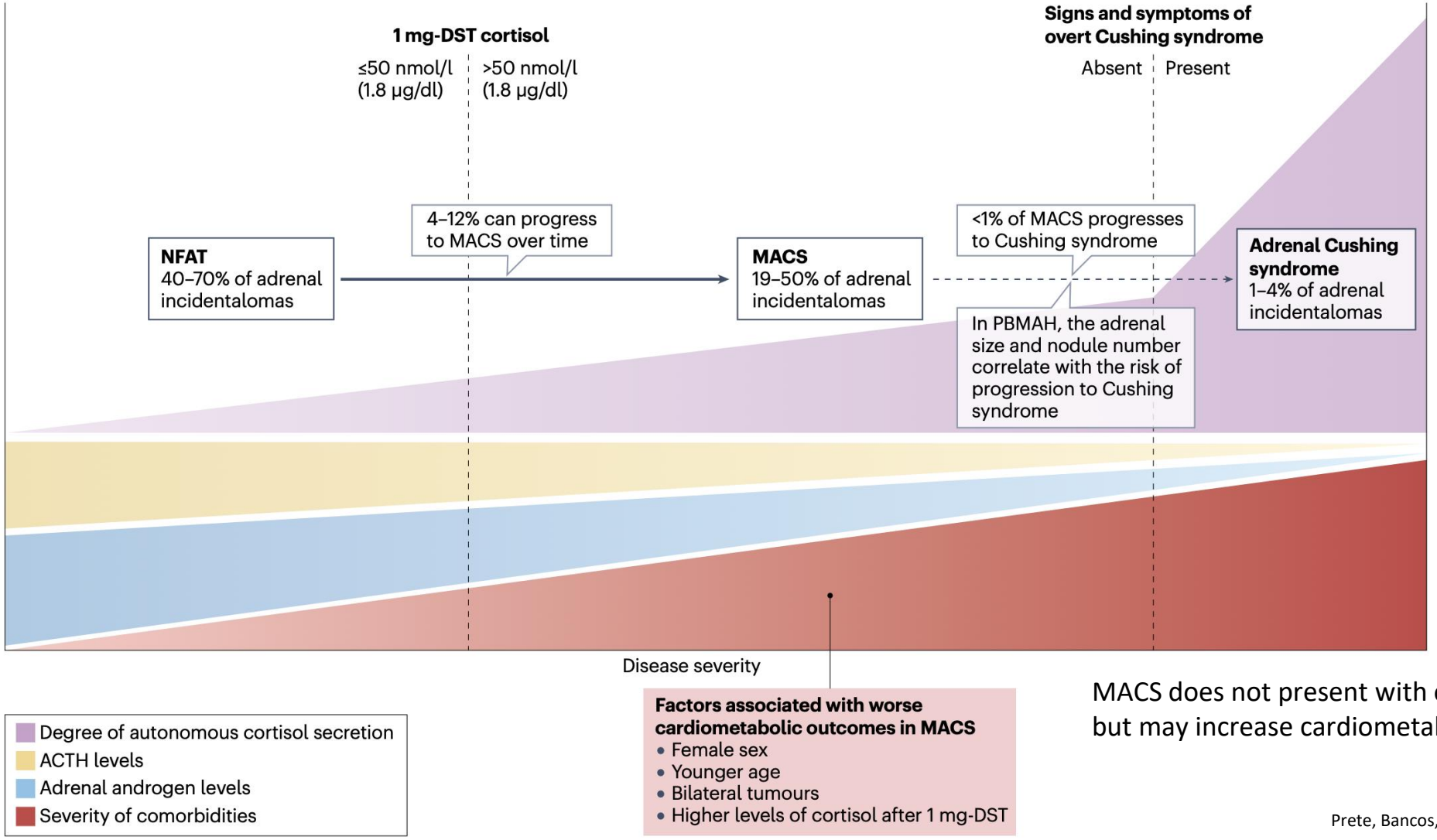
adrenocortical adenomas and mild autonomous cortisol secretion (MACS)



Prete, Bancos, Nature reviews, 2024

Cushing‘s-Syndrome – MACS

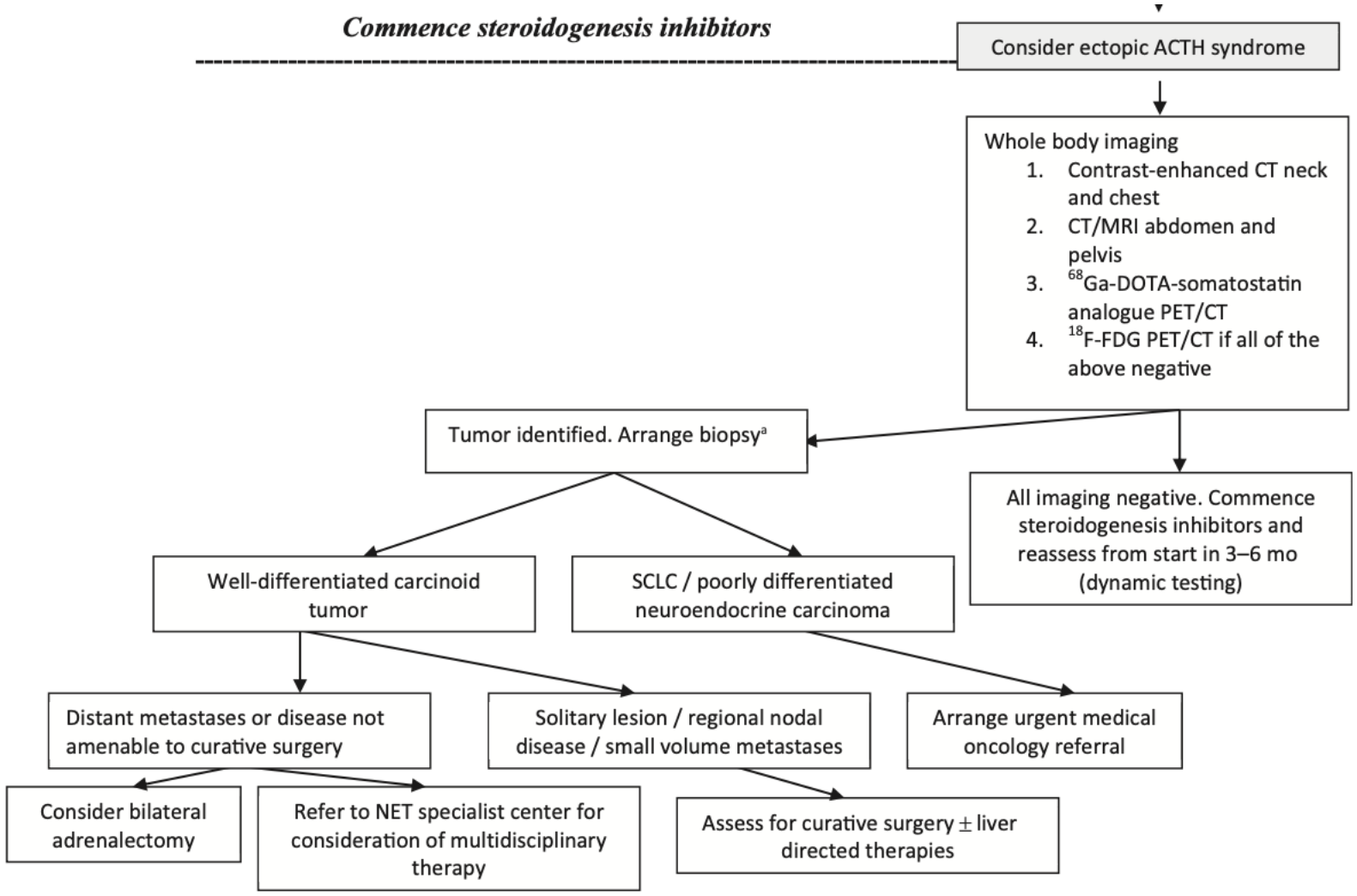
adrenocortical adenomas and mild autonomous cortisol secretion (MACS): Pathophysiology, Comorbidities, management approaches



MACS does not present with overt CS signs but may increase cardiometabolic risk

Prete, Bancos, Nature reviews, 2024

Cushing‘s-Syndrome – Ectopic CS



Hayes, Grossman, EAMC, 2018

Cushing‘s-Syndrome – Ectopic CS

Up to 20%: initial imaging diagnostics without tumor detection

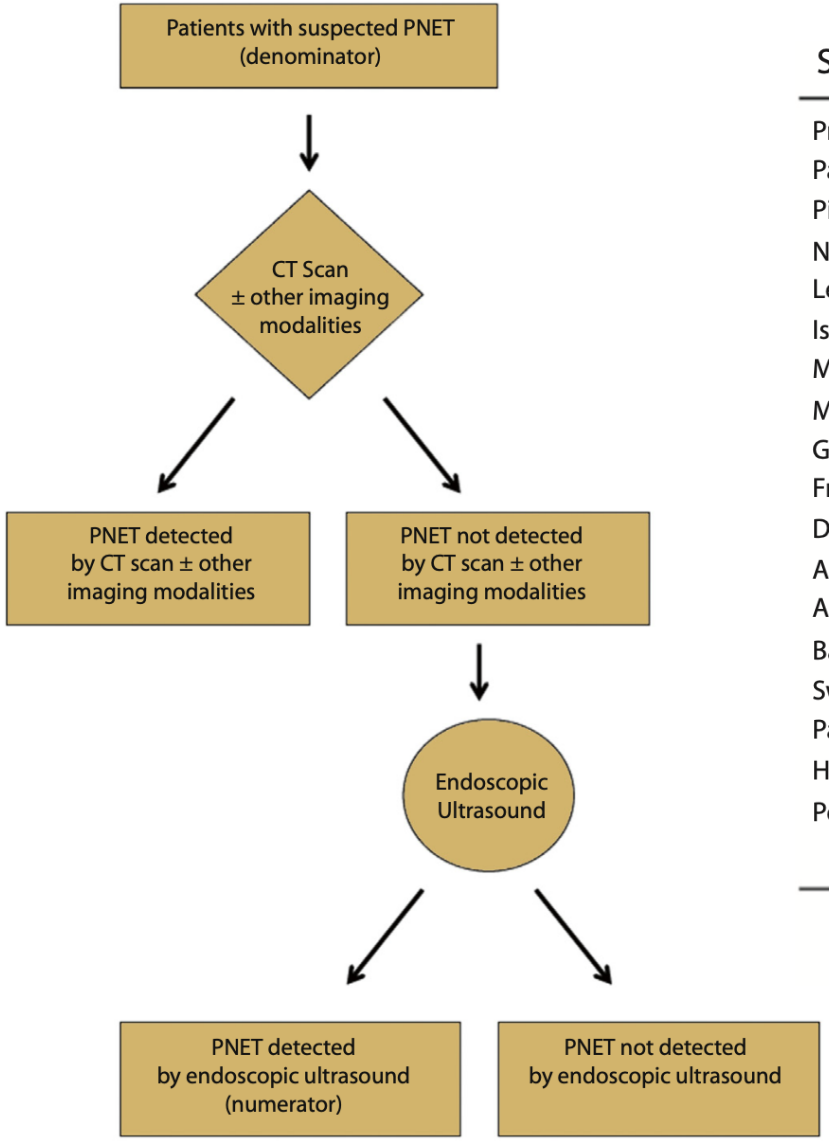
	CT	MRI	OCT	FDG-PET	F-DOPA-PET	MIBG	^{68}Gallium-SSTR-PET/CT
All patients (n = 231)							
Sensitivity, % (95% CI)	66.2% (59.5–72.3)	51.5% (41.9–60.9)	48.9% (41.5–56.3)	51.7% (41.5–61.8)	57.1% (36.6–75.5)	30.8% (12.7–57.6)	81.8% (61.5–92.7)
n	137/207	53/103	84/172	46/89	12/21	4/13	18/22
True positive	63.7%	50.5%	48.3%	51.1%	54.5%	26.7%	78.3%
n	137/215	53/105	84/174	46/90	12/22	4/15	18/23
False negative	33.6%	47.6%	50.6%	47.8%	40.9%	60%	17.4%
n	70/215	50/105	88/174	43/90	9/22	9/15	4/23
False positive	3.7%	1.9%	1.1%	1.1%	4.5%	13.3%	4.3%
n	8/215	2/105	2/174	1/90	1/22	2/15	1/23

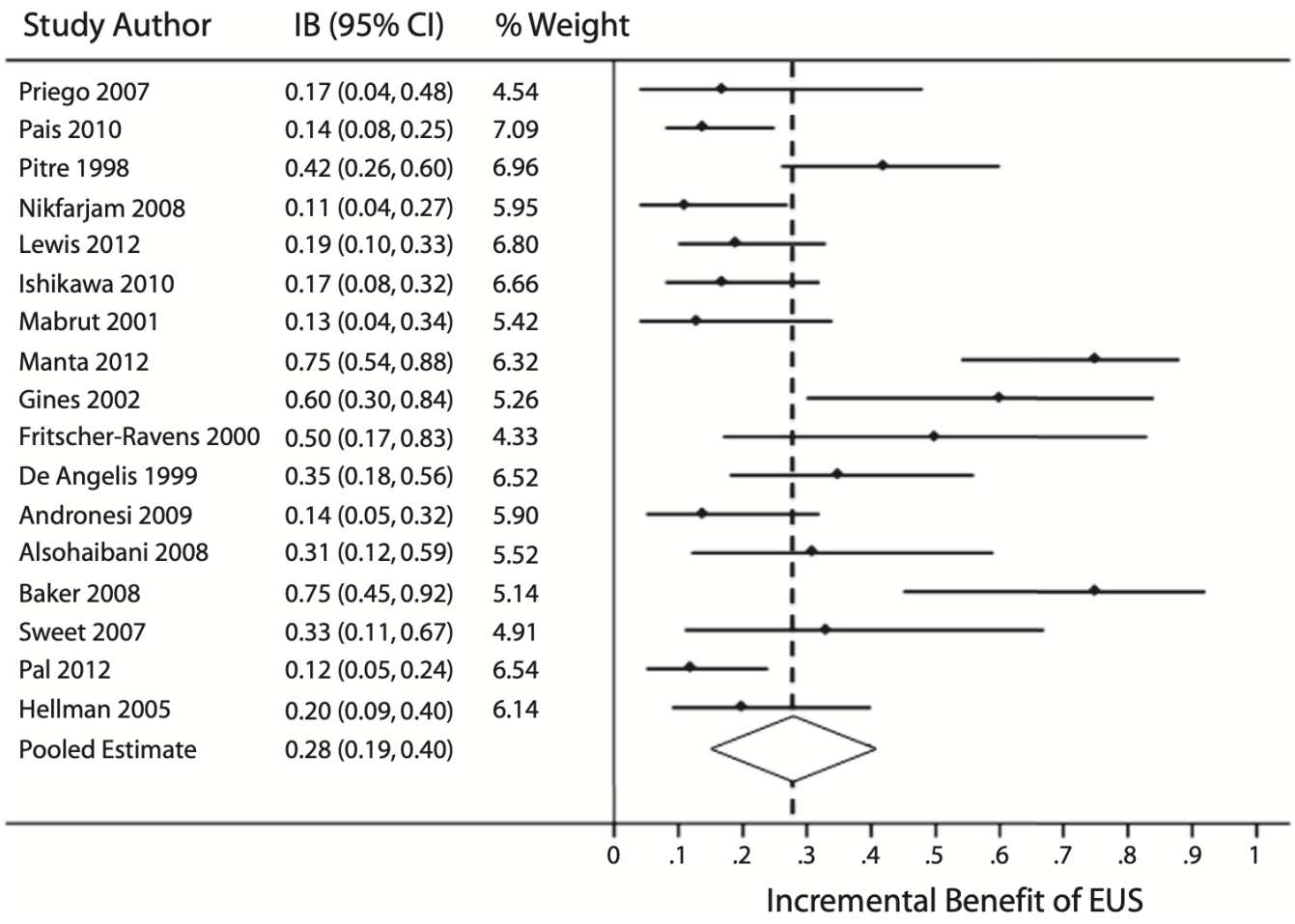
Imaging strategy:

- CT/MRI of the chest, abdomen, and pelvis
- If unrevealing: functional imaging
  - DOTATATE-PET: somatostatin receptor expression
  - FDG-PET / DOPA-PET: metabolically active tumors
  - Octreotide scintigraphy: localize slow-growing carcinoids

Isidori et al., JCEM, 2015

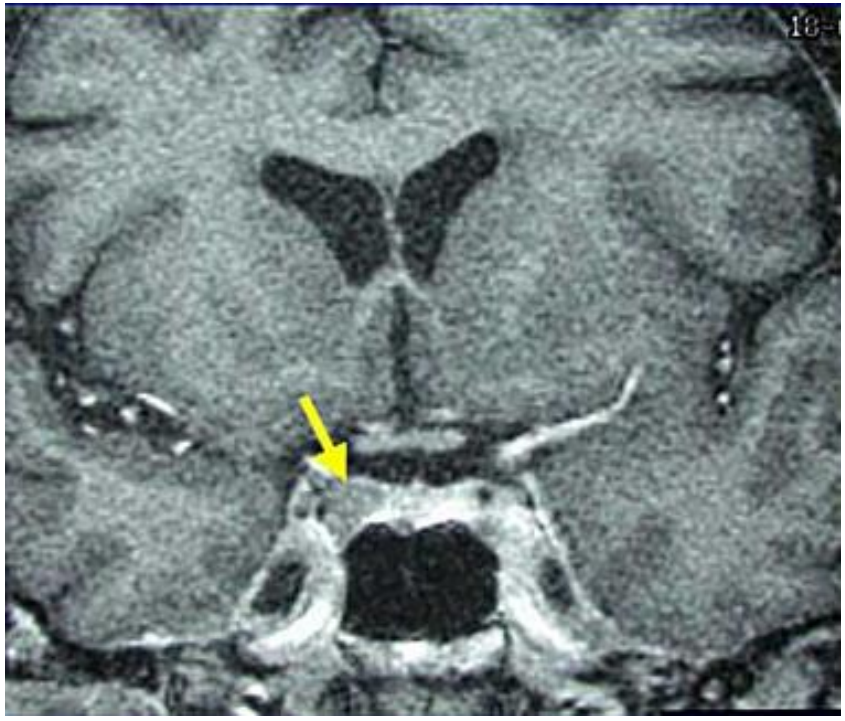
Cushing‘s-Syndrome – PNET





James et al., GE, 2015

Cushing‘s-Syndrome - Imaging: cMRI sella



- cMRI when Cushing's disease is bochemically confirmed!
- Incidentaloma of pituitary gland: up to 10 % of the population
- Detection of adenoma in cMRI: only 60 % in Cushing's disease (proving > 6 mm)
- Gold standard for confirming the diagnosis: bilateral inferior petrosal sinus catheterization

Arnaldi et al., Consensus statement, 2003; http://www.endotext.org

Cushing‘s-Syndrome - Therapy

Treatment of Cushing’s Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, and Antoine Tabarin

J Clin Endocrinol Metab, August 2015, 100(8):2807–2831

Consensus on diagnosis and management of Cushing’s disease: a guideline update *Fleseriu et al., Lancet, 2021*

First-line therapy:

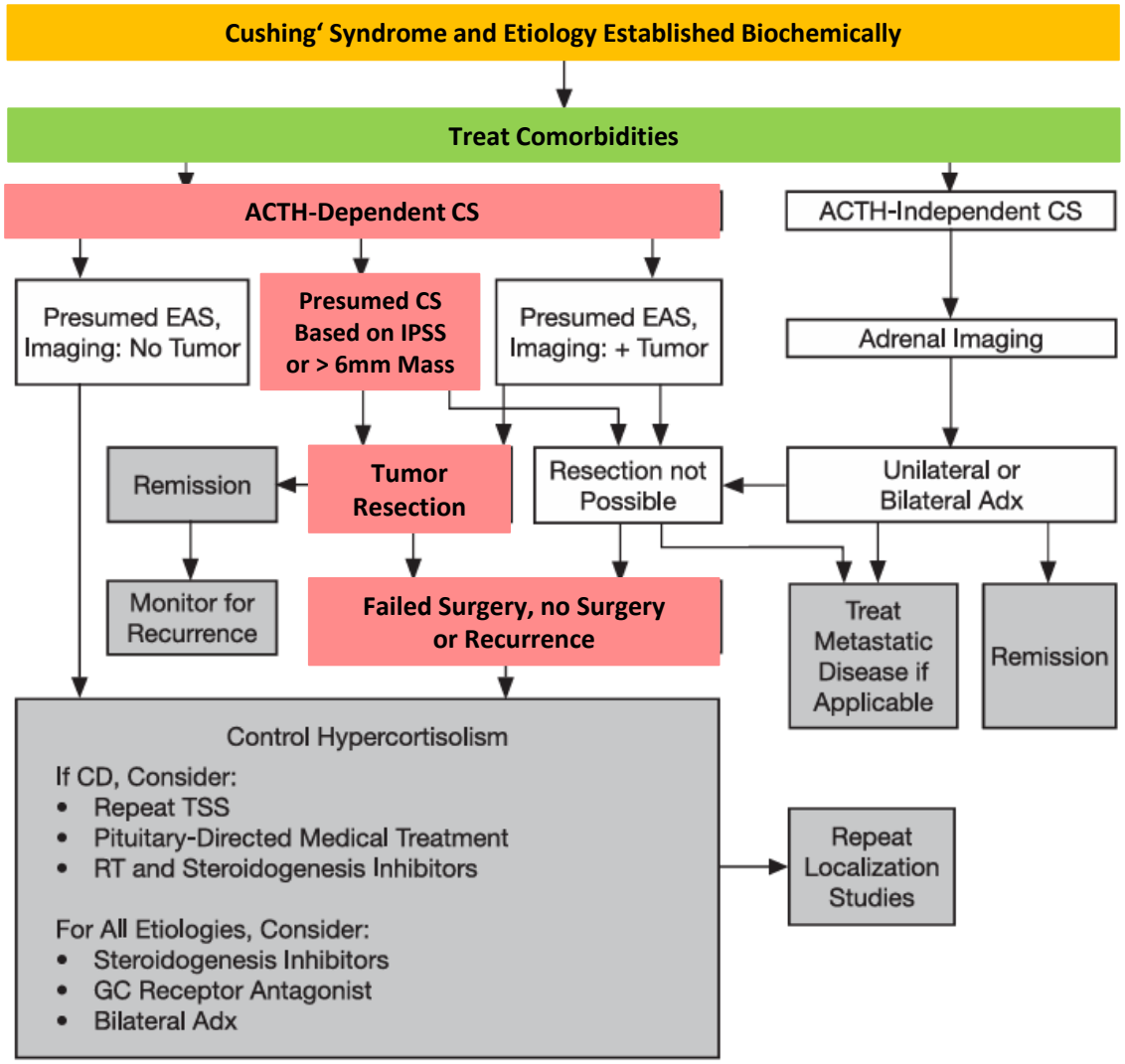
- Transsphenoidal surgery
- Only in specialized centers (> 50 transsphenoidal surgeries/year)

Drug therapy

- **Somatostatin analogs:** Pasireotide
- **Dopamine agonists:** Cabergoline
- **Glucocorticoid receptor antagonist:** Mifepristone
- **Steroid synthesis inhibitors:** Ketoconazole, Mitotane, Levoketokonazole, Metyrapone, Osilodrostat, Etomidate

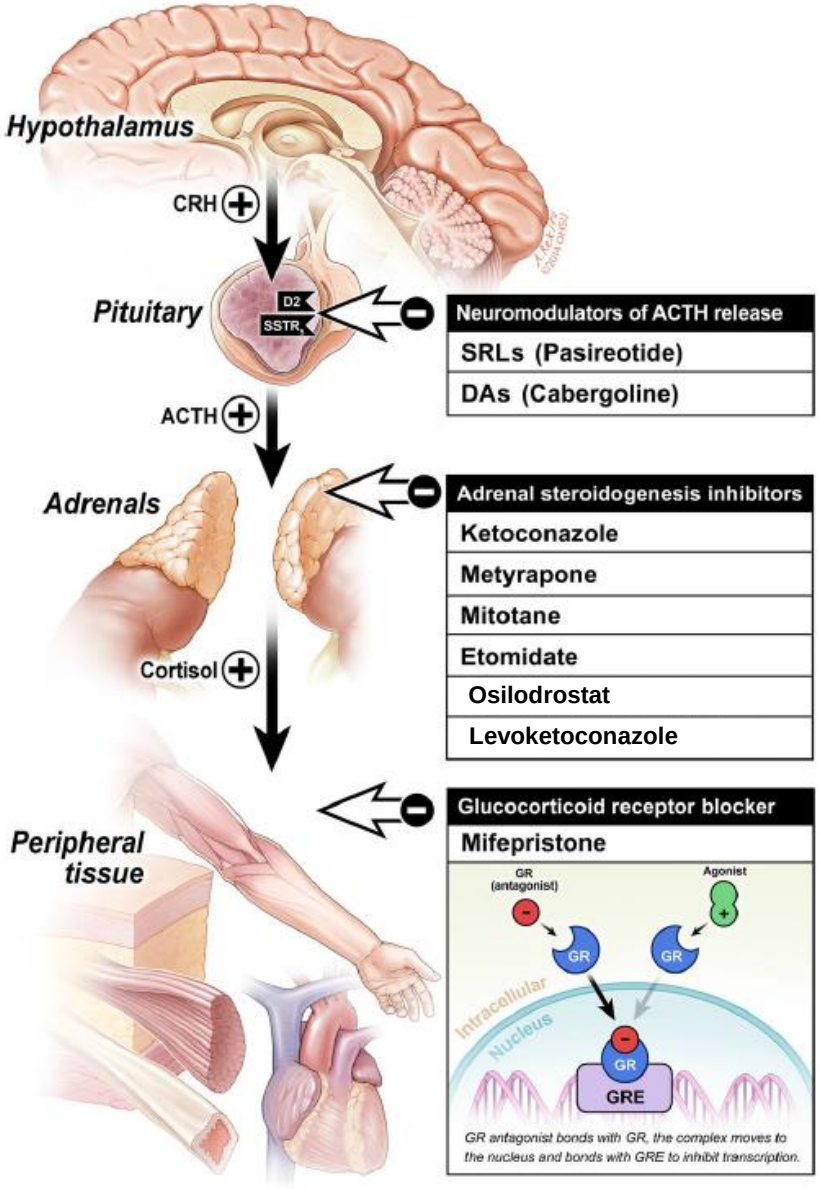
Radiotherapy

Stereotactic single-stage or fractionated radiotherapy



Nieman et al., JCEM, 2015

Cushing‘s-Syndrome - Drug therapy



Indication:

- Preoperative until ready for surgery
- Postoperatively with residual activity
- Parallel use to radiotherapy until onset of action
- If surgery is not possible or not wanted

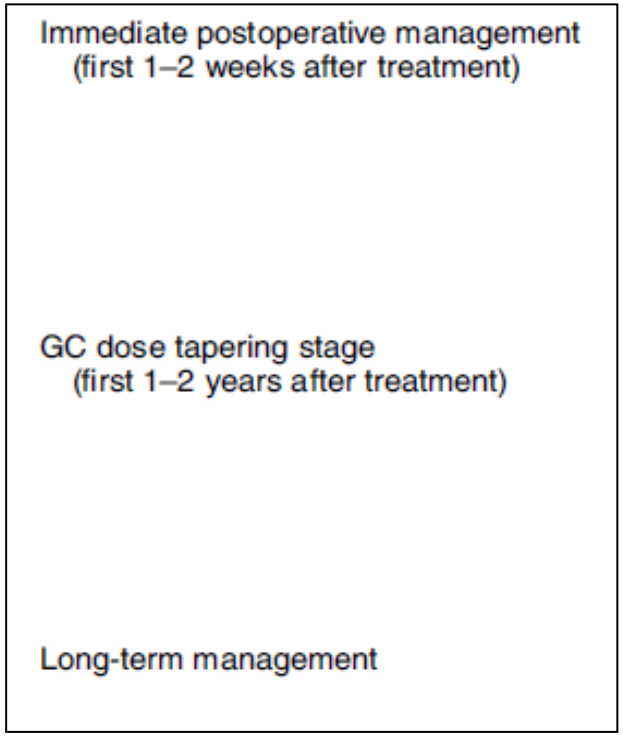
According to S. Hopkins, M. Fleseriu, 2017

Cushing's syndrome - follow-up care

REVIEW
MANAGEMENT OF ENDOCRINE DISEASE

Cushing's syndrome: a structured short- and long-term management plan for patients in remission

Oskar Ragnarsson and Gudmundur Johannsson
Institute of Medicine, Sahlgrenska Academy, University of Gothenburg and Department of Endo Gröna Stråket 8, SE-413 45 Gothenburg, Sweden
(Correspondence should be addressed to O Ragnarsson; Email: oskar.ragnarsson@medic.gu.se)



- ✓ **Annual monitoring of biochemical and clinical Cushing's-associated parameters**
- ✓ **Clinical evaluation of gonadal function, pituitary function tests (LNSC most sensitive), hormone substitution if necessary**
- ✓ **Evaluation of the growth hormone axis (1-2 yrs post-op)**
- ✓ **Longer-term avoidance of supraphysiologic HC dosing**
- ✓ **Evaluation of the cardiovascular risk profile, treatment of arterial hypertension, dyslipidemia and hyperglycemia**
- ✓ **Monitoring bone health and consistent osteoporosis therapy**
- ✓ **Control of cognitive impairment and/or psychiatric disorders (e.g. depression, anxiety disorder)**

Ragnarsson et al., EJE 2013

Cushing's syndrome - Summary

Interpretation of Dynamic Tests in Different Cushing's Etiologies

Test	Cushing's Disease (CD)	Ectopic ACTH	Adrenal CS
CRH Test	↑ ACTH >50%, ↑ Cortisol >20%	No response	ACTH <30 pg/mL
DDAVP Test	↑ ACTH >33%, ↑ Cortisol >18%	No significant response	No response
8 mg Dexamethasone Test	Cortisol suppression >50%	No suppression (or partial)	No suppression
Liddle's Test (16 mg DST)	Cortisol suppression >50%	No suppression	No suppression
Inferior Petrosal Sinus Sampling (IPSS)	Central/peripheral ACTH ratio >3	Ratio <2	Not applicable
Selective Adrenal Venous Sampling (AVS)	Not applicable	Not applicable	Lateralization index ≥2–3 → unilateral disease
Plasma Steroid Profile (+DST/CRH-test)	↑ Cortisol, ↑ ACTH, ↓ 11-deoxycortisol	Variable; ↑ or = 11-deoxycortisol	↑ Cortisol, ↓ ACTH, ↑ 11-deoxycortisol

Cushing's syndrome - Summary

- **Cushing's syndrome** is rare but critical to detect early due to significant **morbidity and mortality**, particularly from cardiovascular and metabolic complications.
- Diagnostic approach must:
  - **Exclude exogenous steroid use**
  - Utilize at least **two initial screening tests**
  - Consider **comorbidities, physiologic hypercortisolism**, and **medication effects**
- **High variability** in test sensitivity/specificity necessitates:
  - Individualized testing strategy based on **clinical presentation**
  - Awareness of **false positives/negatives** due to physiological and pharmacological factors
- Differentiation:
  - **ACTH-dependent** vs. **ACTH-independent** forms based on **ACTH levels and imaging**
  - **CRH-/DDAVP-tests and IPSS** essential for unclear pituitary imaging or borderline cases
- Imaging and dynamic tests guide localization:
  - Pituitary MRI (sensitivity ~60%)
  - CT/MRI abdomen, functional imaging for ectopic sources
- **Therapy**: Surgery is first-line; **medical therapy** plays a role pre-op, post-op, or when surgery is not feasible
- **Follow-up** is lifelong: Monitor for **recurrence, hormonal recovery**, and **management of comorbidities**

Accurate diagnosis and **multidisciplinary management** are crucial to improve long-term outcomes in patients with Cushing's syndrome.

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Thank you for your attention!

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