

Iperensione arteriosa secondaria

10.000 bambini

4%

400

10.000 adulti

40%

4000

Neonati		Età scolare		Adolescenti		Adulti	
Primitiva	0	Primitiva	50	Primitiva	350	Primitiva	3600
Secondaria	400	Secondaria	350	Secondaria	50	Secondaria	400
Coartazione aortica	120	Nefropatie	220	Nefropatie	30	OSAS	120
Renovascolare	100	Coartazione aorta	70	Coartazione aorta	10	Iperaldosteronismo primario	90
Nefropatie	80	Renovascolare	35	Renovascolare	5	Renovascolare	80
Neoplastica	10	Endocrina	15	Endocrina	1	Nefropatie	40
Endocrina	4	Neoplastica	15	Neoplastica	1	Endocrina	20
Altre	...	Altre		Altre		Altre	

TABLE 13. Patient characteristics that should raise the suspicion of secondary hypertension

Younger patients (<40 years) with grade 2 or 3 hypertension or hypertension of any grade in childhood

Sudden onset of hypertension in individuals with previously documented normotension

Acute worsening of BP control in patients with previously well controlled by treatment

True resistant hypertension hypertension

Hypertensive emergency

Severe (grade 3) or malignant hypertension

Severe and/or extensive HMOD, particularly if disproportionate for the duration and severity of the BP elevation

Clinical or biochemical features suggestive of endocrine causes of hypertension

Clinical features suggestive of atherosclerotic renovascular disease or fibromuscular dysplasia

Clinical features suggestive of obstructive sleep apnea

Severe hypertension in pregnancy (>160/110 mmHg) or acute worsening of BP control in pregnant women with preexisting hypertension

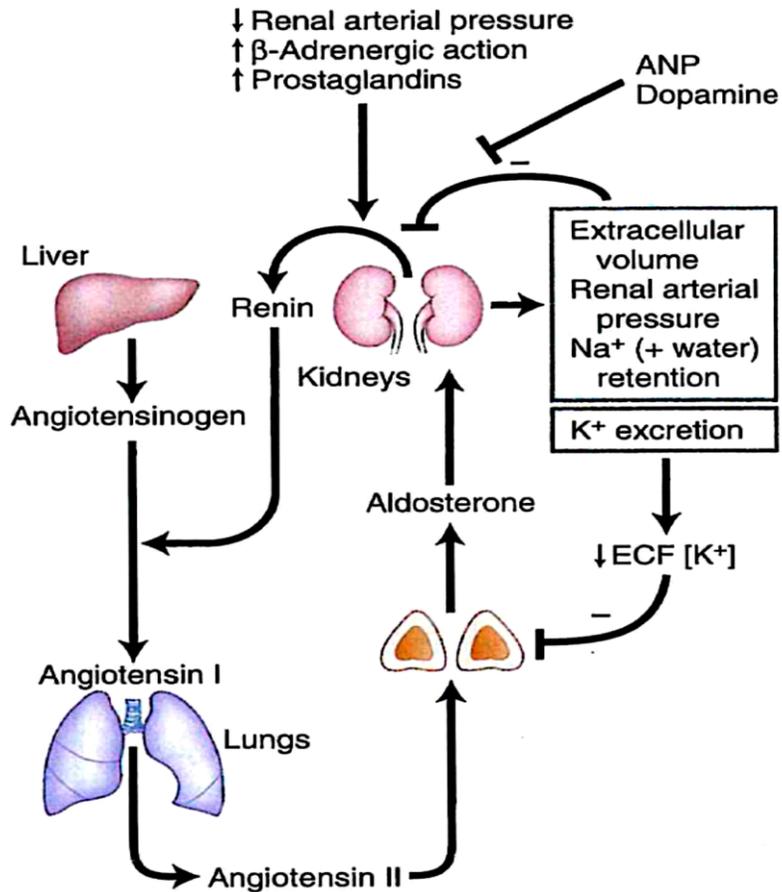
Cause endocrine di ipertensione secondaria

Patologie surrenaliche	Iperaldosteronismo primario	Sporadico, familiare (tipo1-5)
	Feocromocitoma	Sporadico (60%), genetico (40%)
	Ipercortisolismo endogeno ACTH-indipendente	Adenomi, carcinomi, iperplasia (PPNAH, AIMAH)
	Eccesso deossicorticosterone	Deficit 11 β -idrossilasi 17 α - idrossilasi Neoplasia DOC secernente Resistenza cortisolo
Patologia extrasurrenalica	Distiroidismo	Tireotossicosi/Ipotiroidismo
	IperPTH	
	Ipercortisolismo endogeno ACTH-dipendente	Malattia Cushing o ACTH ectopico
	Acromegalia	
	Pseudoiperaldosteronismo	Difetto 11 β HSD2 AME acquisita (liquerizia) Sindrome di Liddle

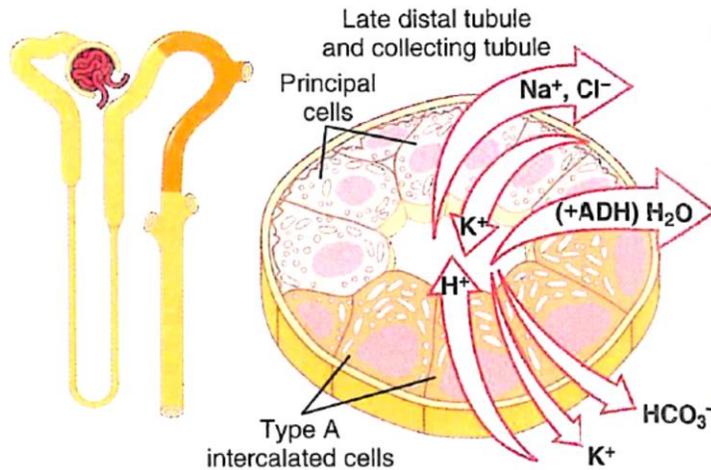
Cause endocrine di ipertensione secondaria

		SCREENING
Patologie surrenaliche	Iperaldosteronismo primario (20%)	ARR
	Feocromocitoma	Metanefrine
	Ipercortisolismo endogeno ACTH-indipendente	1mg-DEX, 24h UFC, LNSC
	Eccesso deossicorticosterone	Ipokaliemia alcalosi steroidi
Patologia extrasurrenalica	Distiroidismo	TSH, FT4
	IperPTH	Calcio fosforo, PTH, 25OHvitD
	Ipercortisolismo endogeno ACTH-dipendente	1mg-DEX, 24h UFC, LNSC
	Acromegalia	IGF-1
	Pseudoiperaldosteronismo	Ipokaliemia alcalosi steroidi

Iperaldosteronismo primario



B Regulation of aldosterone secretion



CELLULE PRINCIPALI DEL TUBULO DISTALE e DOTTO COLLETTORE

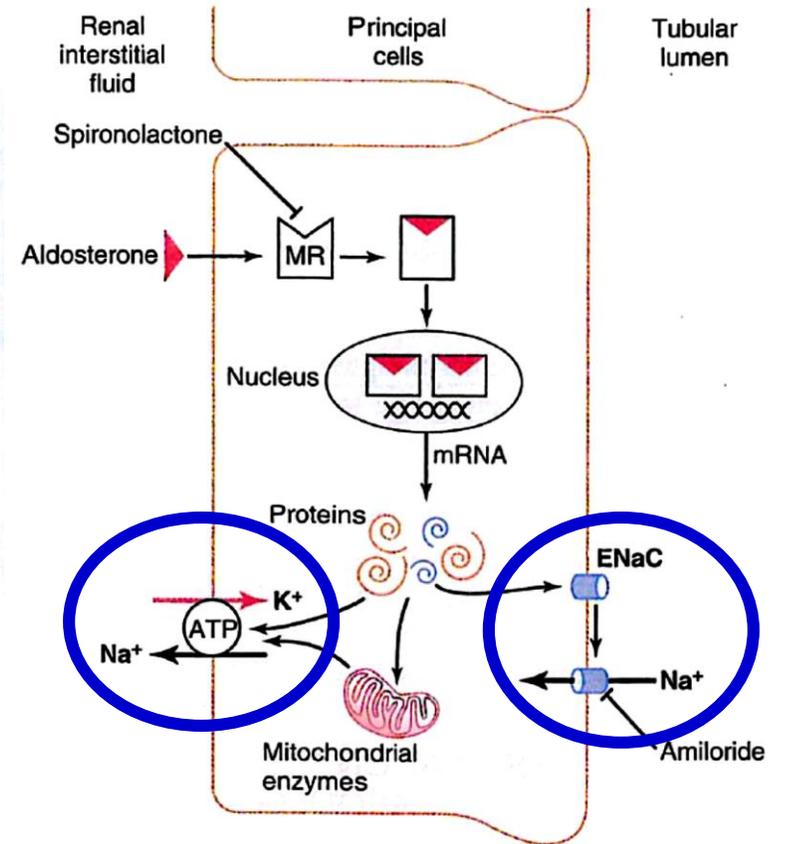
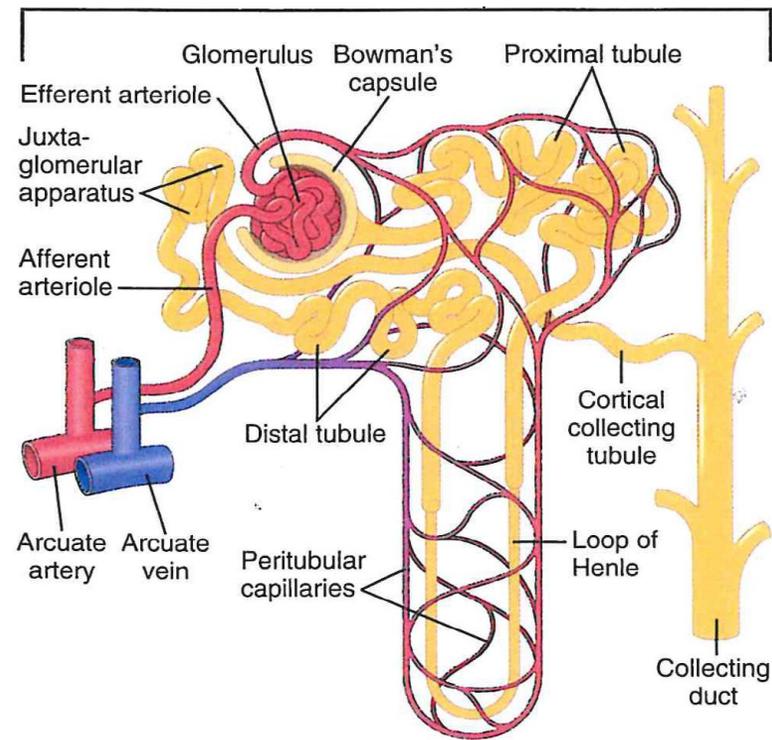


Figure 78-4. Aldosterone-responsive epithelial cell signaling pathways. Activation of the mineralocorticoid receptor (*MR*) by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block epithelial sodium channel proteins (*ENaC*).



Ormone	Sito di Azione	Effetti
Angiotensina II	Tubulo prossimale, branca ascendente ansa Henle dotto collettore	↑ riassorbimento di sodio e acqua ↑ eliminazione H ⁺
Aldosterone	Tubulo e dotto collettore	↑ riassorbimento di sodio (e acqua) ↑ eliminazione K ⁺ H ⁺
ADH	Tubulo distale , tubulo e dotto collettore	↑ riassorbimento di acqua
ANP	Tubulo distale , tubulo e dotto collettore	↓ riassorbimento di sodio

ECCESSO di ALDOSTERONE

Aumenta il riassorbimento di sodio ma osmolalità si mantiene costante – per

1. Attivazione ADH/SETE;
2. NATRIURESIS da PRESSIONE (aldosterone escape)

Aumenta l'eliminazione di potassio che causa ipokaliemia e di idrogenioni che causa alcalosi

DIFETTO di ALDOSTERONE

La carenza di aldosterone porta alla perdita di grandi quantità di sodio e con esse di liquidi, che in assenza di terapia porta al collasso cardiocircolatorio in 3-14 giorni (in caso di mancata secrezione).

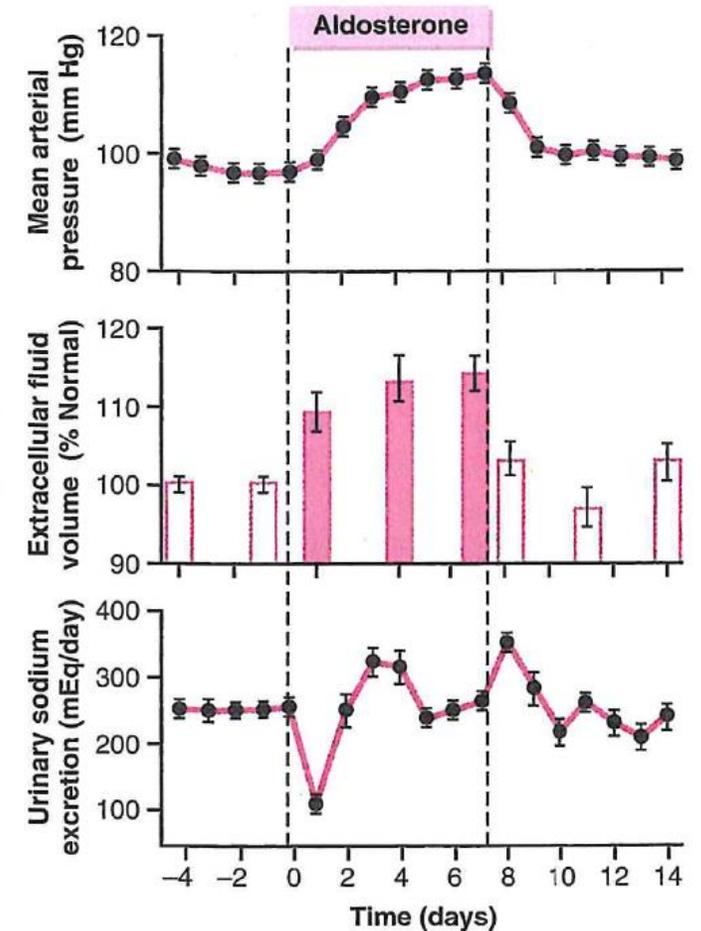


Figure 78-3. Effect of aldosterone infusion on arterial pressure, extracellular fluid volume, and sodium excretion in dogs. Although aldosterone was infused at a rate that raised plasma concentrations to about 20 times normal, note the "escape" from sodium retention on the second day of infusion as arterial pressure increased and urinary sodium excretion returned to normal. (Data from Hall JE, Granger JP, Smith MJ Jr, et al: Role of hemodynamics and arterial pressure in aldosterone "escape." *Hypertension* 6[suppl 1]:1183-1192, 1984.)

SINDROME CONN

La sindrome di Conn è una malattia causata da un eccesso di mineralocorticoidi (aldosterone) o **iperaldosteronismo primitivo**.

Essa è stata descritta per la prima volta nel **1955** da **Jerome W Conn**, in una *giovane donna di 34 anni che si presentava per astenia, spasmi muscolari, ipertensione arteriosa e ipokaliemia e che veniva riscontrata affetta da un aldosteronoma, adenoma zona glomerulosa del surrene*.

L'iperaldosteronismo primitivo ha una prevalenza che varia dal 5.9 al 6.8% nella popolazione generale, arrivando fino al **12% nei pazienti con ipertensione** e **20% nei pazienti con ipertensione resistente**.

L'iperaldosteronismo primitivo può avere diverse cause tra cui: **adenoma** unilaterale o bilaterale, iperplasia surrenalica, carcinoma corticosurrene (pazienti giovani con masse voluminose). Tra le forme **rare, genetiche**, ricordiamo il GRA *glucocorticoid-remediable aldosteronism* (rara) legata alla fusione di CYP11B1 e CYP11B2.

L'iperaldosteronismo porta a eliminazione renale di potassio e aumentato riassorbimento di sodio con conseguenti **ipokaliemia**, espansione del volume extracellulare e **ipertensione**. Alcalosi (per aumentata eliminazione di idrogenioni a livello renale). Astenia e spasmi muscolari (muscolo non si riesce a depolarizzare e contrarre). Stipsi.

4. Come identificare le forme genetiche

Nei giovani pazienti con diagnosi di IP, specialmente quelli con familiarità per IP e/o *ictus* in età < 40 anni, dovrebbero essere considerate, confermate o escluse le forme familiari o genetiche di IP (tabella 4).

Tabella 4	
Forme genetiche di IP	
Tipo	Mutazione e descrizione
FH-I	IP sopprimibile con glucocorticoidi, forma autosomica dominante dovuta alla presenza di un gene chimerico ibrido, per ricombinazione tra i geni <i>CYP11B1</i> e <i>CYP11B2</i> , che codifica un enzima in grado di sintetizzare l'aldosterone sotto controllo di ACTH.
FH-II	Da mutazioni del gene <i>CLCN2</i> , codificante per il canale del cloruro CIC-2.
FH-III	Da mutazioni del gene <i>KCNJ5</i> , che codifica per il canale del potassio Kir 3.4.
FH-IV	Da mutazioni nel gene <i>CACNA1H</i> , che codifica per il canale del calcio Cav 3.2.
PASNA	IP con crisi epilettiche e anomalie neurologiche, da mutazioni del gene <i>CACNA1D</i> , che codifica per il canale del calcio CaV 1.3.

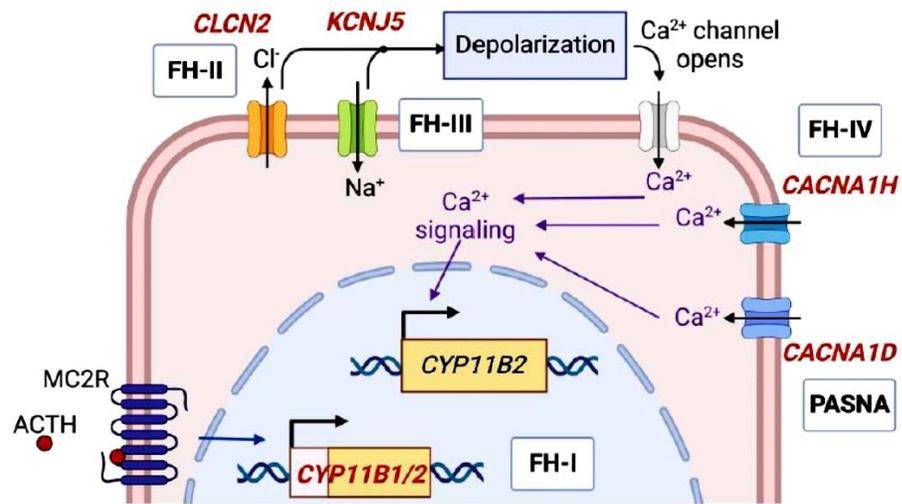
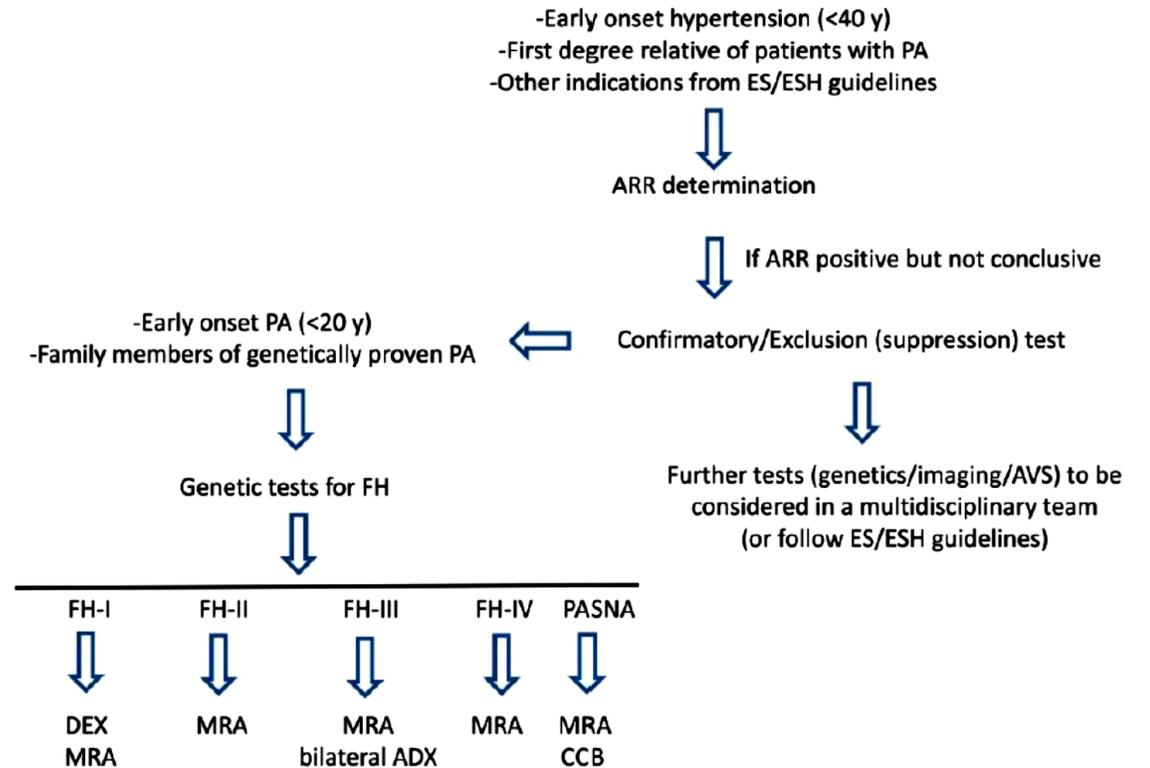


Figure 1. Pathophysiology of FH. In FH-I, a hybrid gene (*CYP11B1/CYP11B2*) causes aberrant expression of an enzyme with aldosterone synthase activity in the zona fasciculata under the control of ACTH. In FH-II, pathogenic variants in *CLCN2* lead to increased chloride efflux, and in FH-III, pathogenic variants in *KCNJ5* render the encoded potassium channel permeable to sodium ions. In both FH-II and FH-III, the resulting membrane depolarization causes voltage-gated calcium influx. *CACNA1H* pathogenic variants in FH-IV and *CACNA1D* pathogenic variants in PASNA syndrome directly increase calcium influx. Calcium is the main signal for aldosterone production in the zona glomerulosa.⁹ Created with BioRender.com. FH, familial hyperaldosteronism.



Gianluca, M, 48 anni

giunge in ambulatorio per **incidentaloma surrenalico con ipertensione arteriosa resistente.**

PA 145/90 mmHg in terapia con nebivololo/idroclortiazide 5/25 mg, ramipril 10 mg, amlodipina 10 mg.

TC addome (controllo post nefrectomia per ca cellule chiare 3 anni prima) nodulo surrene destra di 1 cm densità <10HU.

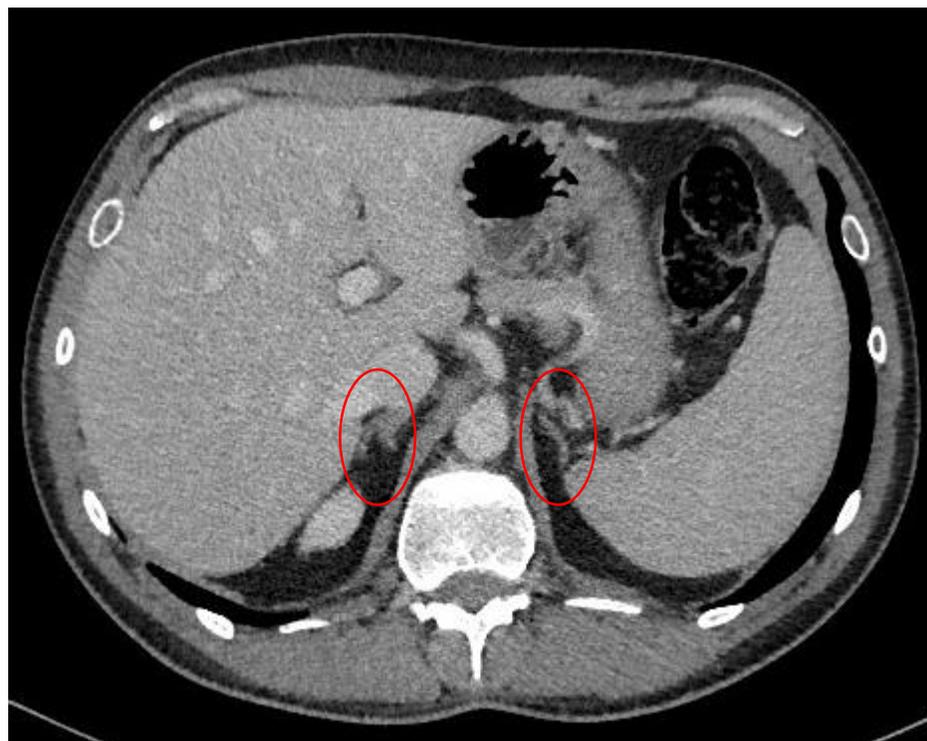
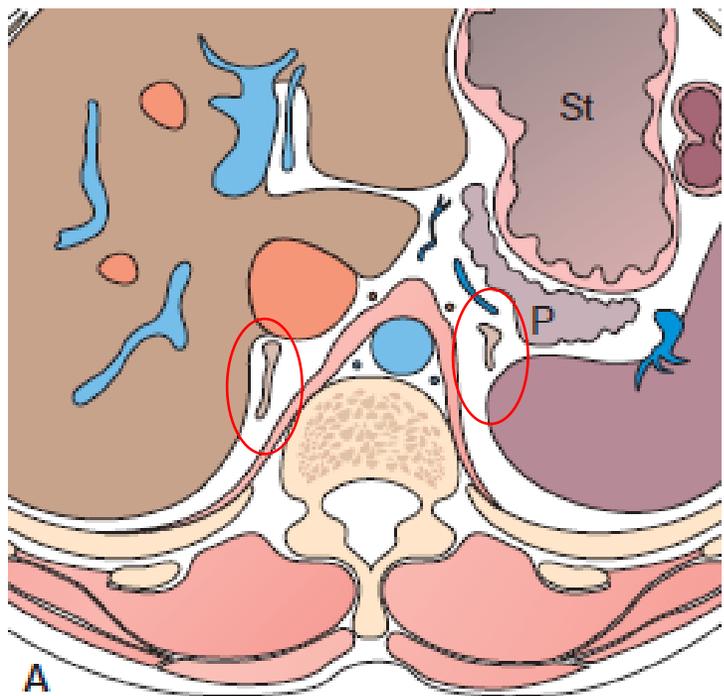
LADA

Fratture vertebrali (D4,D5,D10) traumatiche.

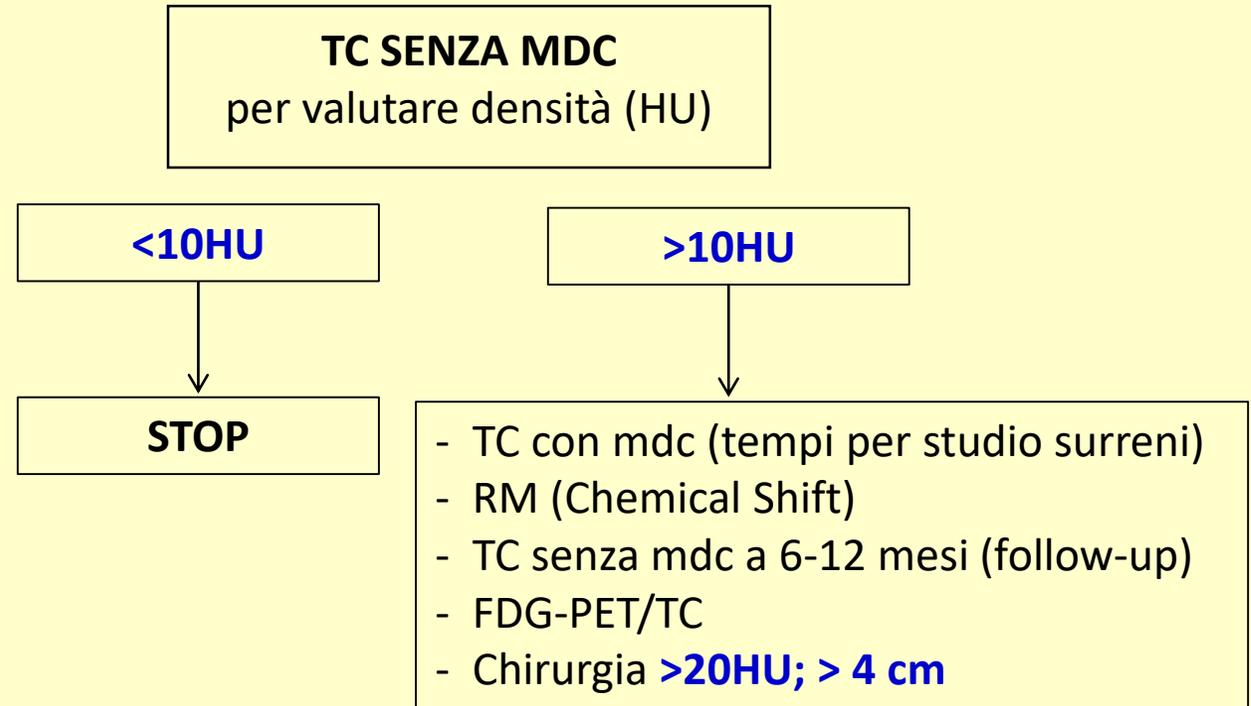
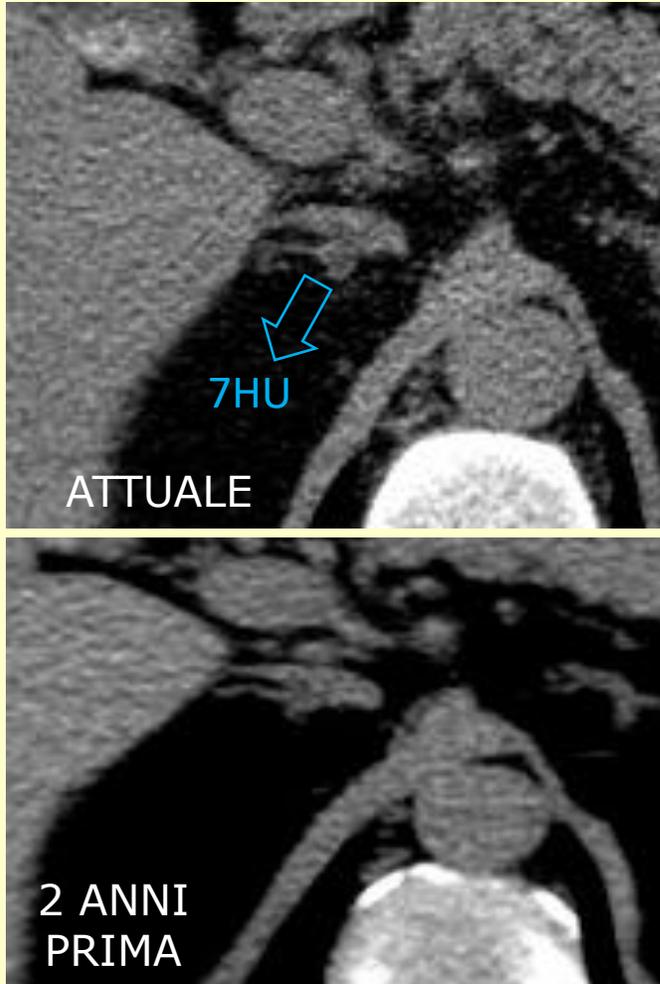
Table 1

Categories of patients where the screening for primary aldosteronism is recommended.

Condition	Description
Severe hypertension	Hypertension stage 3, i.e. systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg
* Resistant hypertension	Blood pressure values that remain above goal in spite of concurrent use of three antihypertensive agents of different classes. If tolerated, one of the three agents should be a diuretic, and all agents should be prescribed at maximum recommended (or maximally tolerated) antihypertensive doses.
Patients with hypertension associated with (permanent or intermittent) spontaneous or diuretic-induced hypokalemia	Serum potassium (K^+) < 3.5 mmol/L in absence of other potential causes of hypokalemia (i.e. gastrointestinal disorders, abuse of licorice, etc.).
* Hypertension or hypokalemia associated with adrenal incidentaloma	Hypertensive patients with an adrenal mass detected on imaging.
Normal potassium levels (≥ 3.5 to ≤ 5.0 mmol/L) associated with another of the above-mentioned indications for PA screening	
When hypertension-mediated organ damage and cardiovascular or renal morbidity are more severe than expected from the level and duration of hypertension	Hypertension-mediated organ damage such as microalbuminuria, renal disease, hypertensive retinopathy, left ventricular hypertrophy and diastolic dysfunction, etc.
Hypertension and sleep apnea	See 'Comorbidities' section for further explanations.
Hypertension and atrial fibrillation	See 'Comorbidities' section for further explanations.
Hypertension and a family history of early onset hypertension and/or cerebrovascular accident at a young age (< 40 years) and of first-degree relatives with primary aldosteronism	See 'Testing for familial forms of primary aldosteronism and detection of genetic mutations' for further explanations.
Newly-presenting patients with hypertension and a high chance of cure with adrenalectomy, as, for example, young, women, with a short duration of hypertension	



1. Definizione natura incidentaloma



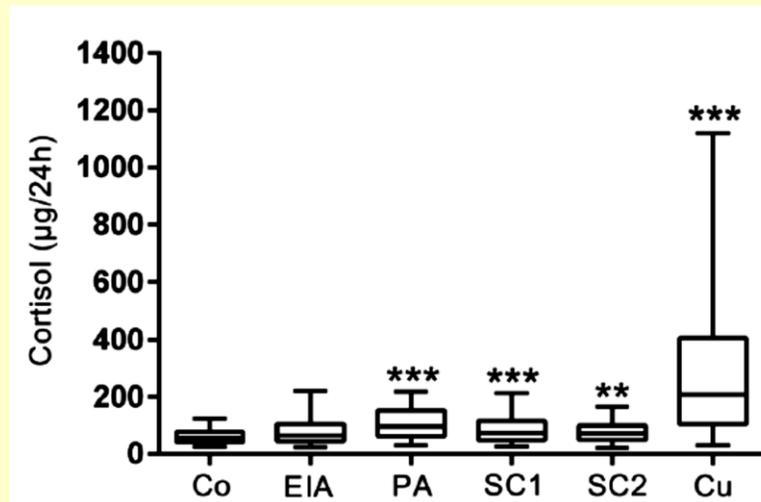
Extra-adrenal malignancy. Younger patients with a history of malignancy are more likely to have a metastasis. (...) Nevertheless, adrenal lesions characterized as benign by noncontrast CT require no further imaging FU.

2. Test di screening: ARR (e non solo)

Esame	Esito	Valori di riferimento
Aldosterone	26.4 ng/dL	1.5-15
Renina	0.5 uU/mL	2.8-40
ARR	559	< 2.06 (ARR-App)
Potassio	3.53 mEq/L	3.5-5.10
Cortisolo 1 mg DEX	0.74 ug/dL	<1.8

PRIMA di misurare ARR:

- Correggere ipokaliemia
- Normale intake sodico
[considerare sodiuria e potassiuria 24h]
- Sospendere bloccanti RAAS, diuretici, β bloccanti NSAIDs EP per 4 settimane

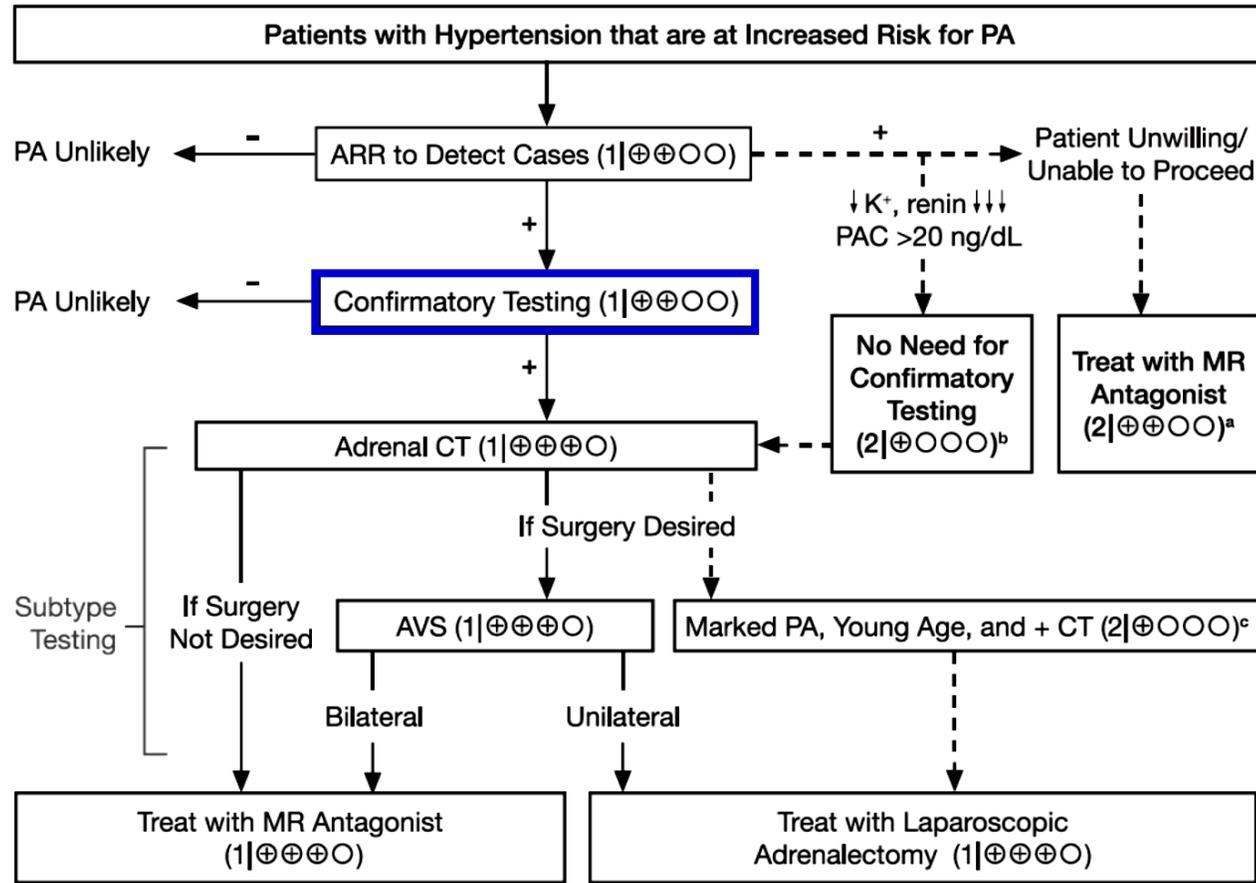


In patients with adrenal incidentalomas, a 1mg DEX <1.2 µg/dl rules out postsurgical hypocortisolism

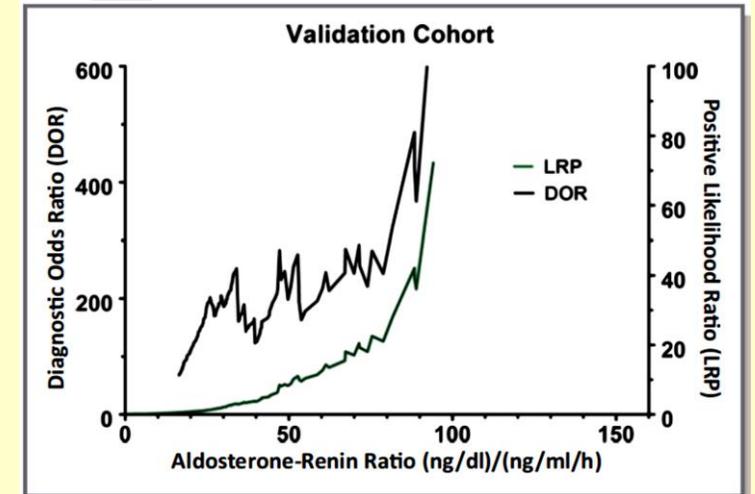
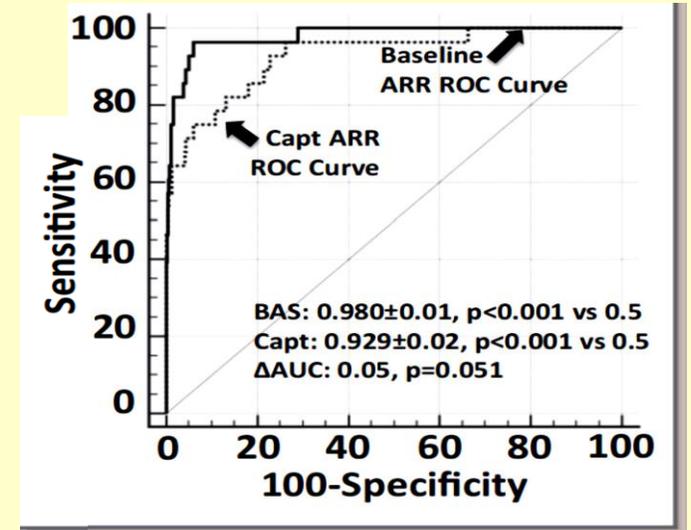
Eller-Vainicher C, J Endocr Soc 2020

Arlt W, JCI Insight 2017

3. Test di conferma iperaldosteronismo primario



Aldosterone dopo salina 18 ng/dL < 5 ng/dL assente



4. Adrenal vein sampling

10 good reasons why adrenal vein sampling is the preferred method for referring primary aldosteronism patients for adrenalectomy

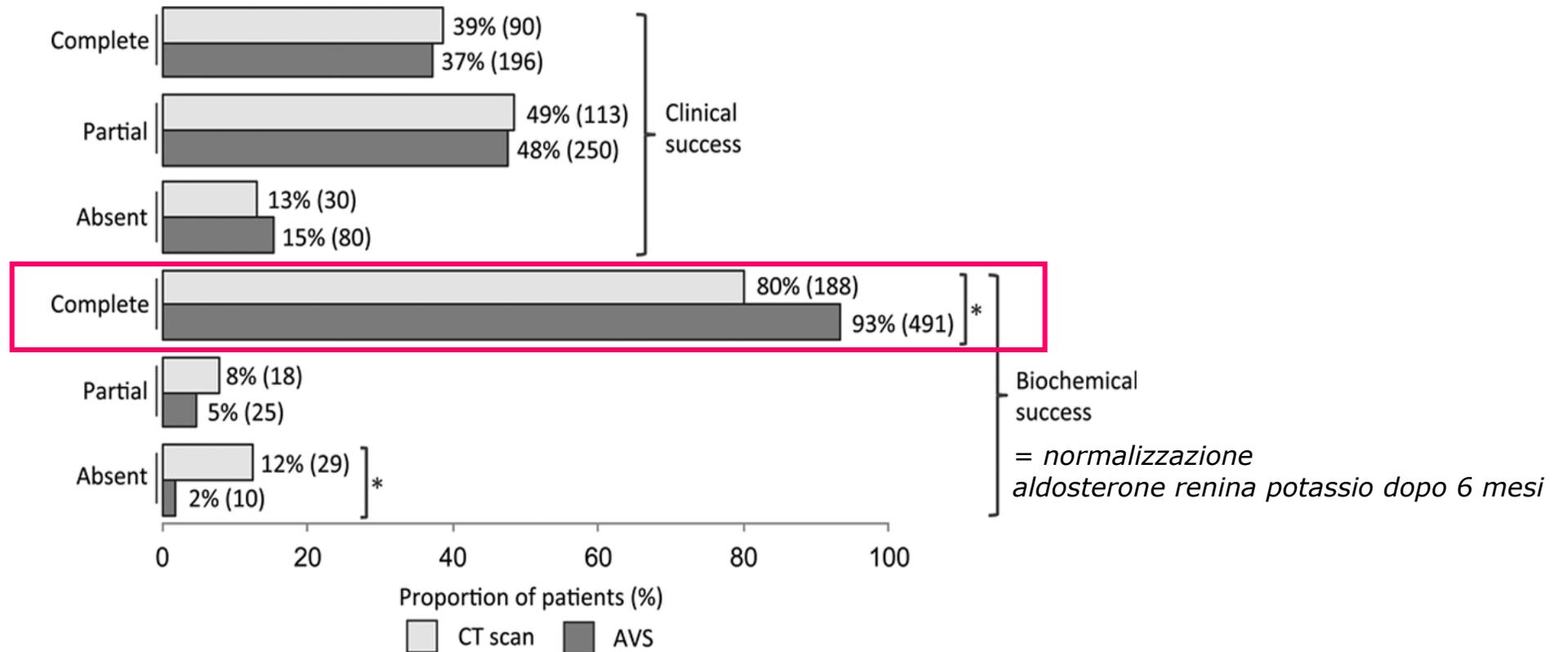
Gian Paolo Rossi^{a,b}, Paolo Mulatero^c, and Fumitoshi Satoh^d

- 1. Lack of specificity of the adrenal masses** – even when an adrenal lump is visible on imaging in many cases the primary aldosteronism is sustained by one, or more, smaller, and CT-invisible nodules not even reaching 5 mm in maximal diameter
- 2. Safety** AVS is safe, the rate of complications being in the range of 0.5-0.6% (hematomas and adrenal vein rupture)

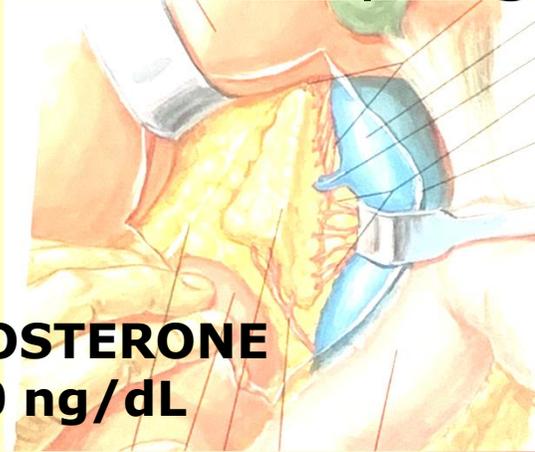
Primary Aldosteronism

Computed Tomography and Adrenal Venous Sampling in the Diagnosis of Unilateral Primary Aldosteronism

Tracy A. Williams, Jacopo Burrello, Leonardo A. Sechi, Carlos E. Fardella, Joanna Matrozova, Christian Adolf, René Baudrand, Stella Bernardi, Felix Beuschlein, Cristiana Catena, Michalis Doumas, Francesco Fallo, Gilberta Giacchetti, Daniel A. Heinrich, Gaëlle Saint-Hilary, Pieter M. Jansen, Andrzej Januszewicz, Tomaz Kocjan, Tetsuo Nishikawa, Marcus Quinkler, Fumitoshi Satoh, Hironobu Umakoshi, Jiří Widimský Jr, Stefanie Hahner, Stella Douma, Michael Stowasser, Paolo Mulatero,* Martin Reincke*



4. Adrenal vein sampling



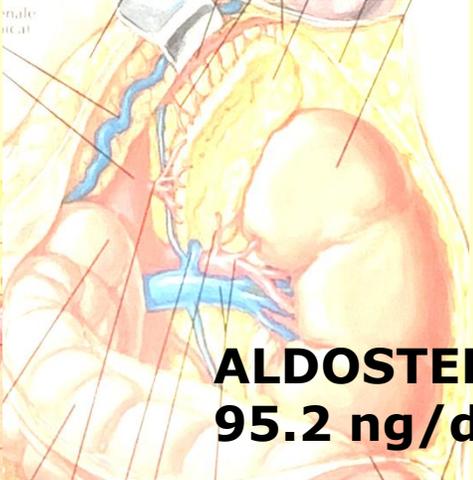
ALDOSTERONE
9780 ng/dL

CORTISOLO
1076 µg/dL

A/C dx=9



CORTISOLO
5.47 µg/dL



ALDOSTERONE
95.2 ng/dL

CORTISOLO
563 µg/dL

A/C sin= 0,17

- 1. SELECTIVITY INDEX.** ADRENAL VEIN TO PERIPHERAL VEIN CORTISOL RATIO. $SI \geq 2$ unstimulated ≥ 3 during cosyntropin stimulation [dosare *metanefrine o androstenedione se cosecrezione cortisolo*]
- 2. ALDOSTERONE LEVELS** are NORMALIZED TO CORTISOL (A/C)
- 3. LATERALIZATION INDEX (LI).** Each side A/C ratio is divided by the other. **LI** between 2-4 under unstimulated conditions, and 2.6-4 during cosyntropin stimulation

Primary hyperaldosteronism is a frequent and potential curable cause of hypertension.

Screening requires ARR and subtyping requires adrenal vein sampling

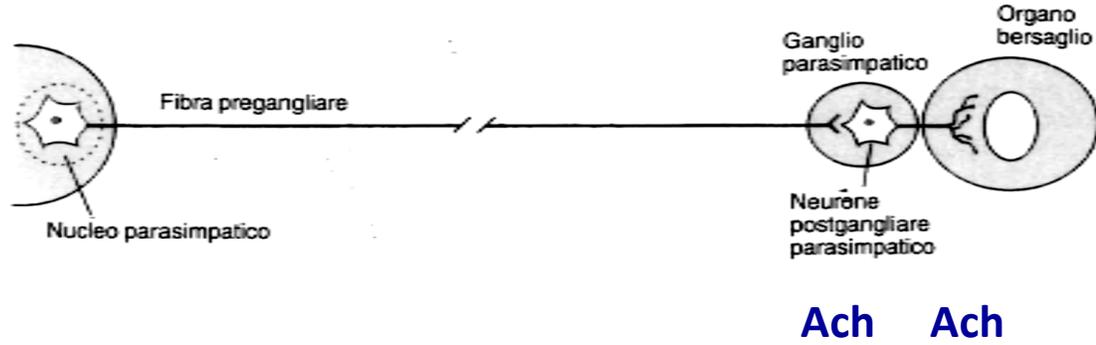
On the whole, available evidence support the view that **AVS-guided unilateral laparoscopic adrenalectomy** should be the preferred option of treatment, while medical treatment is indicated in bilateral adrenal hyperplasia or when identification of unilateral failed.

Mineralocorticoid receptor antagonists are recommended in order to normalize BP and obtain normokalemia when medical treatment is chosen. Plasma renin levels can be used as a guide to the appropriate dosing of medication. Instructing the patient to diminish sodium intake or introducing amiloride is a strategy to spare MRA and control side effects.

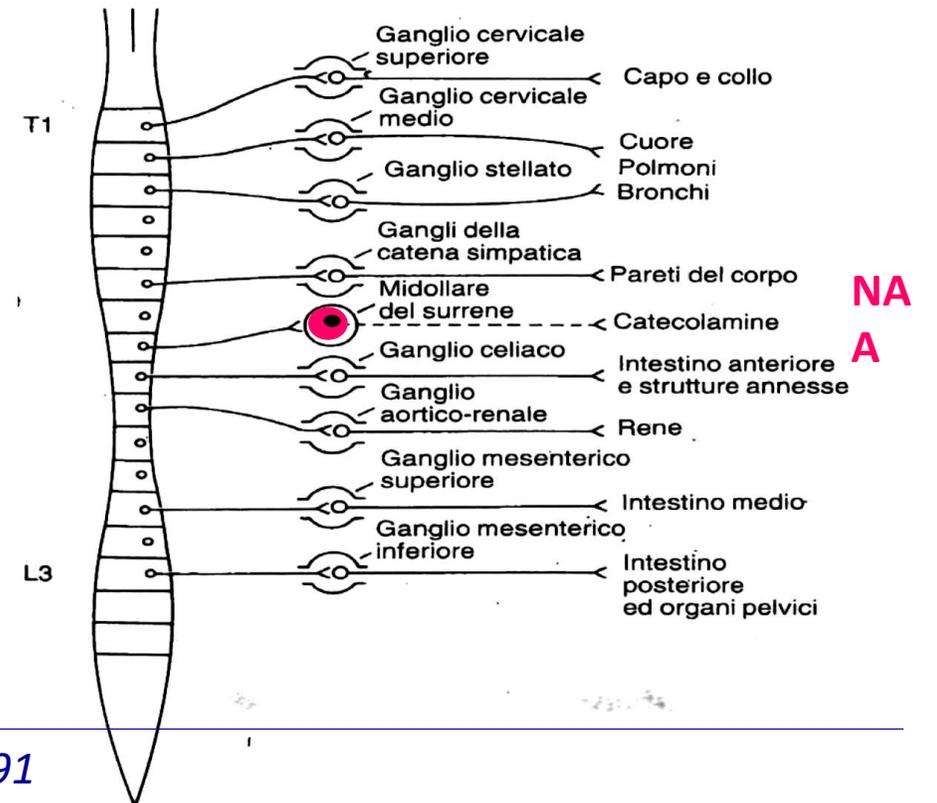
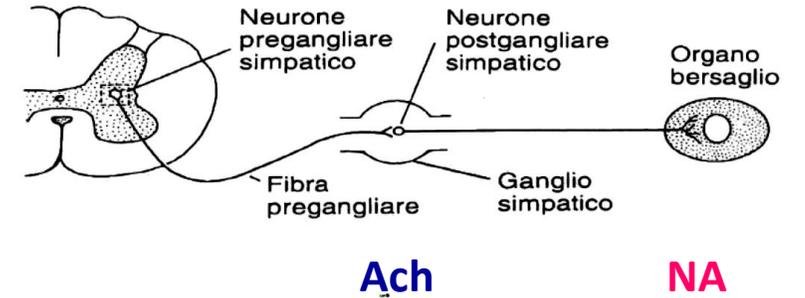
This allows to control blood pressure, and prevent or regress organ damage and associated comorbidities.

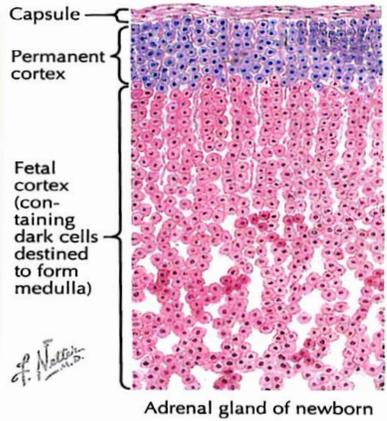
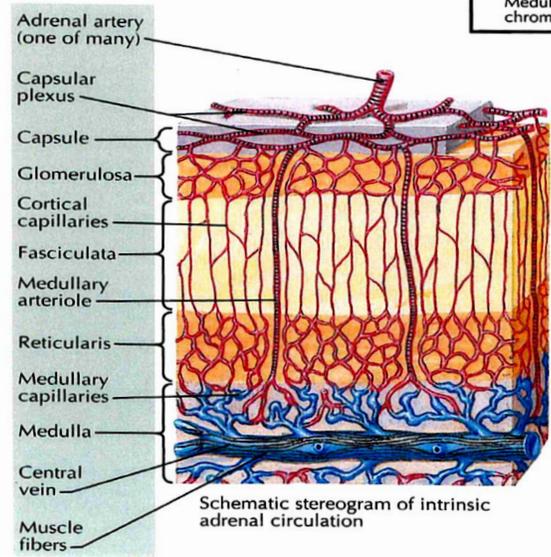
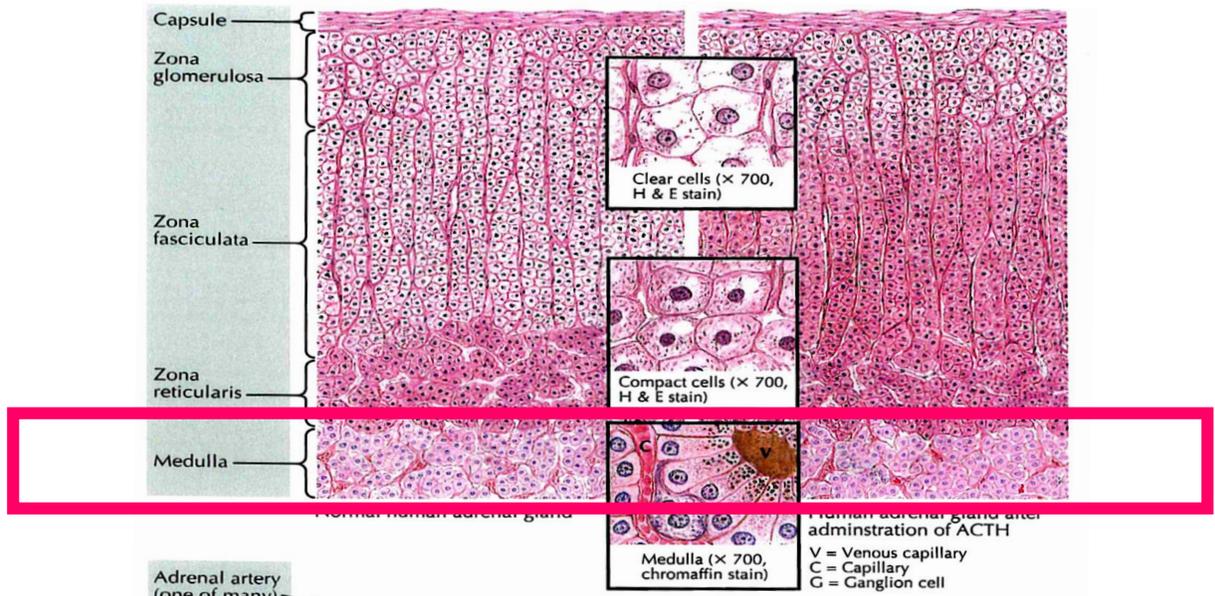
PHEO/PPGL

HNPGL

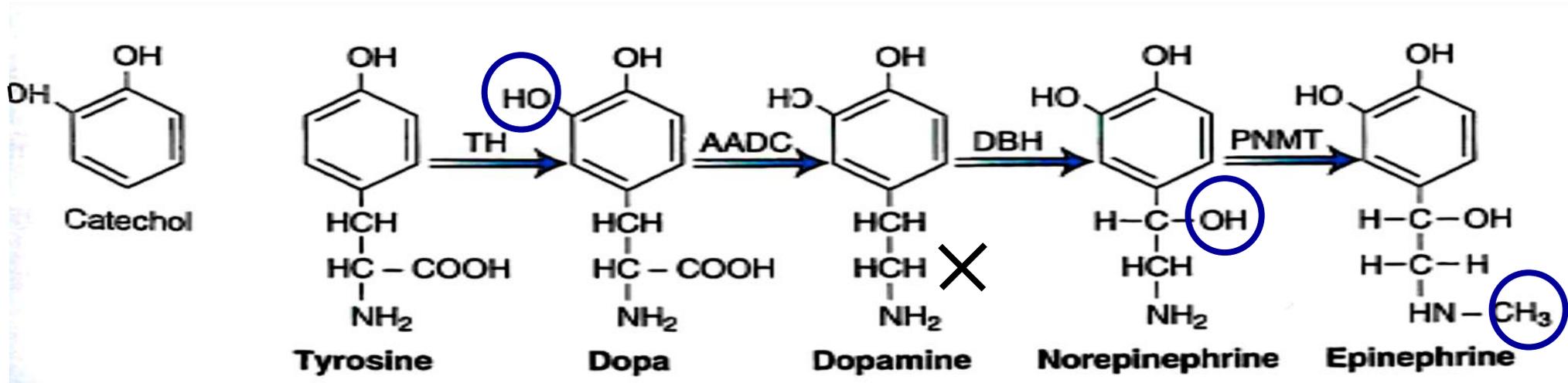


PPGL





TERMINAZIONI NERVOSE



-
 Eccesso NA e A
 +
 Difetto NA e A
 Cortisolo
 cAMP
 Protein-kinasi calcio dipendenti

**Tirosina
 idrossilasi**

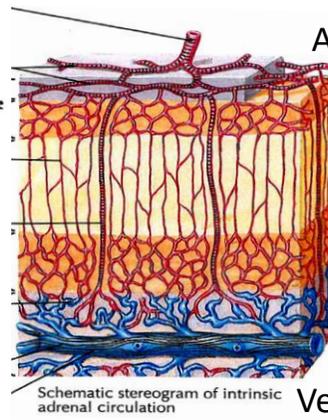
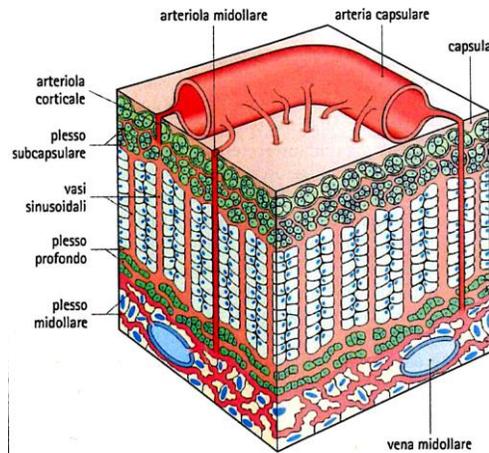
Dopa
 decarbossilasi

Dopamina
 idrossilasi

**Metil-
 transferasi**

+
 Cortisolo

MIDOLLARE



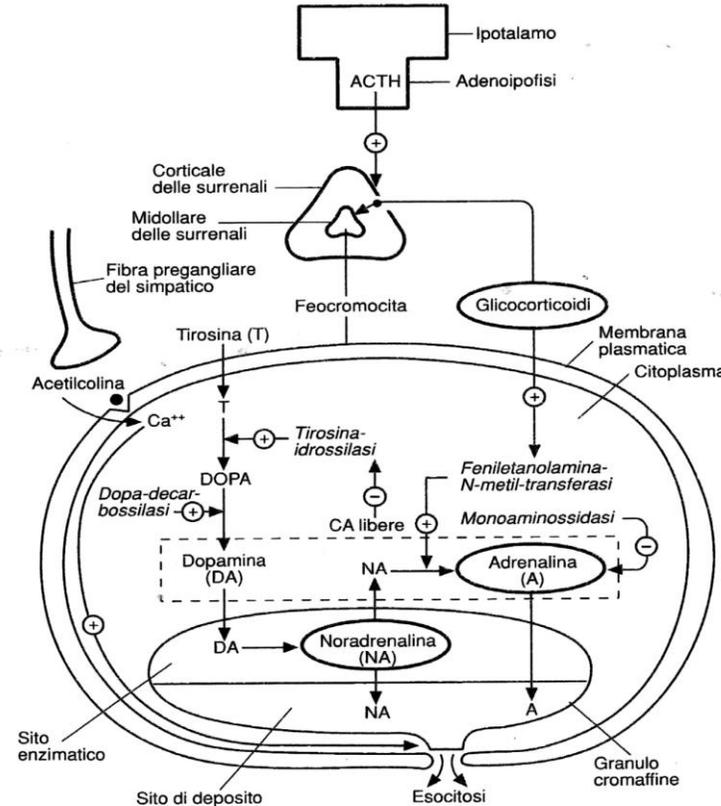
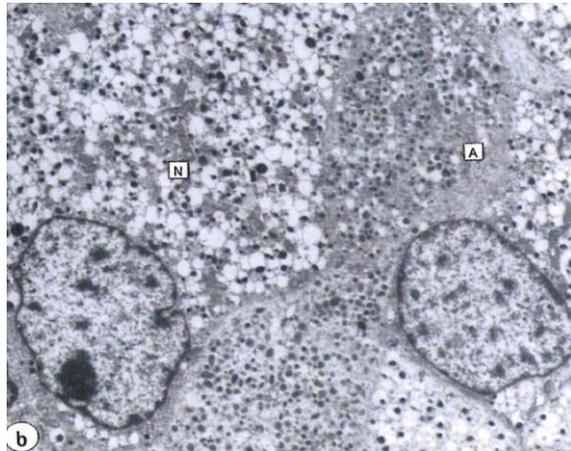
Arteria diaframmatica inferiore, aorta, arteria renale

SISTEMA PORTALE

Rapido effetto cortisolo su midollare

Vena surrenalica destra – cava

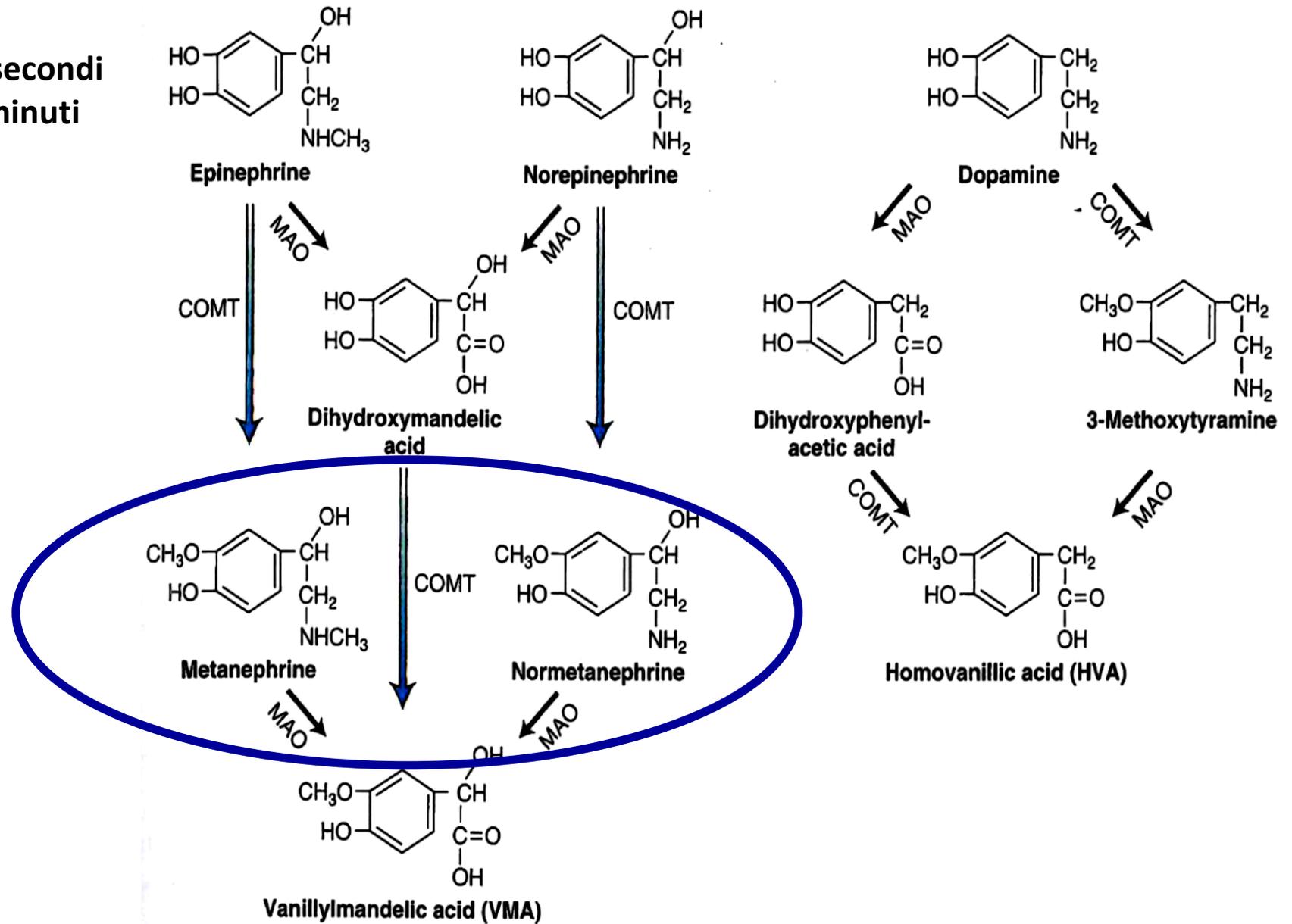
Vena surrenalica sinistra – vena renale cava

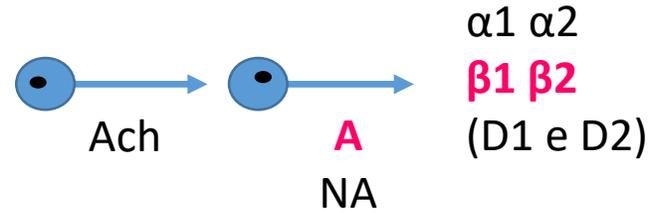
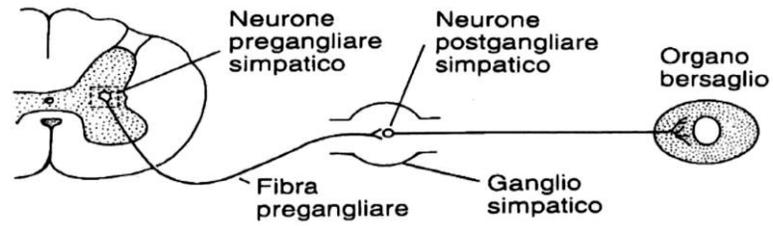


A - 0.2 ug/kg/min (80%)
NA - 0.05 ug/kg/min (20%)

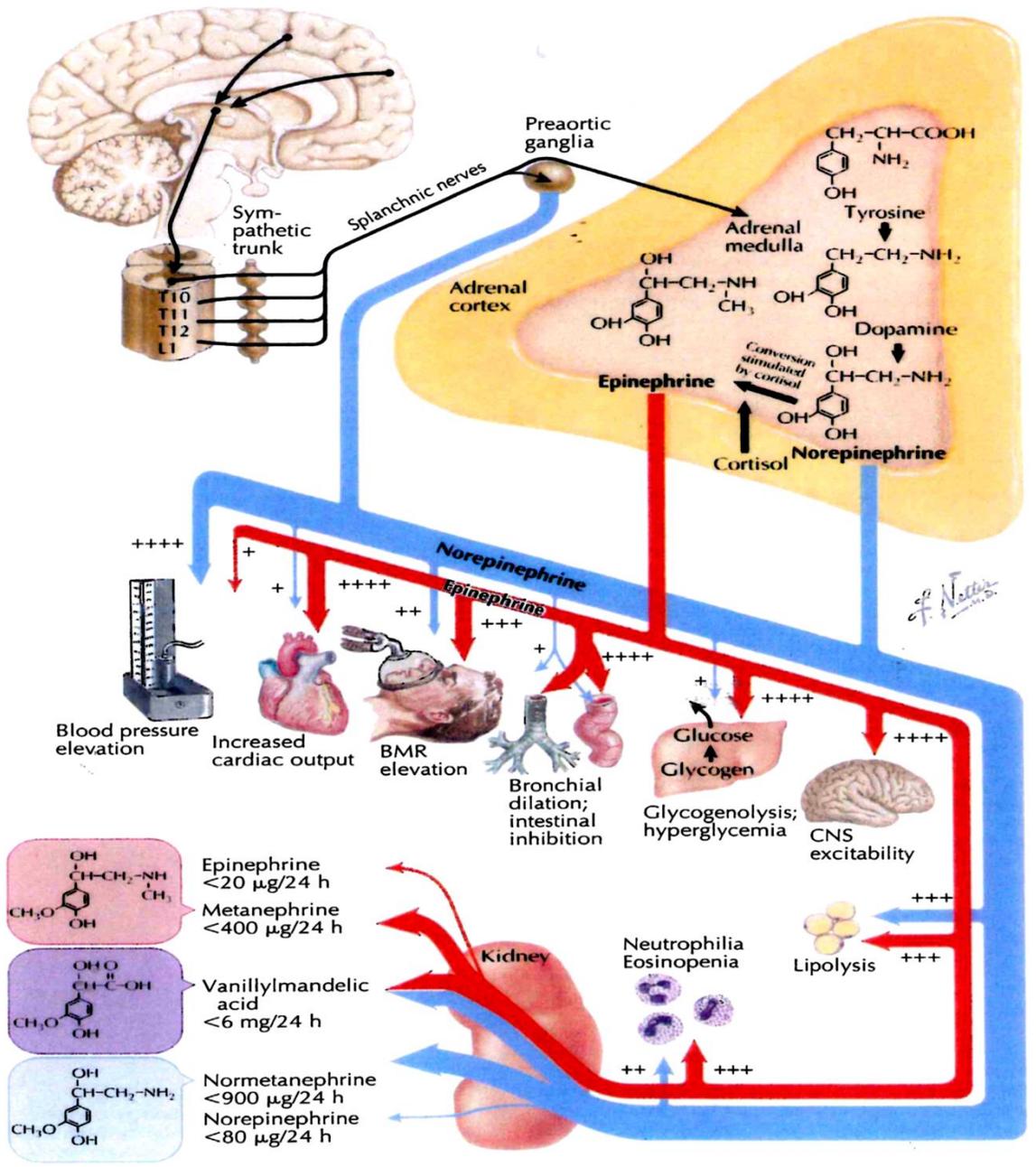
90% di NA e A vengono internalizzate dalle terminazioni nervose (uptake 1 – **bloccato COCAINA**)
 10% di NA e A vengono internalizzate da altre cellule (uptake 2)

**EMIVITA 10-100 secondi
RIMOSSE in 2-4 minuti**

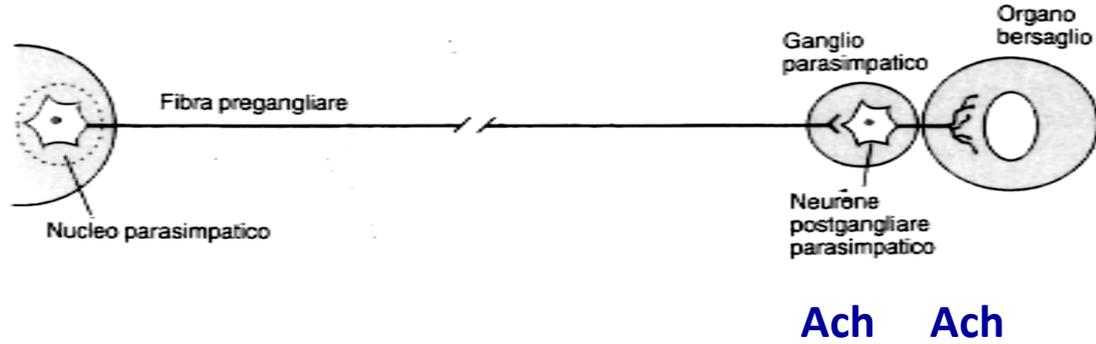




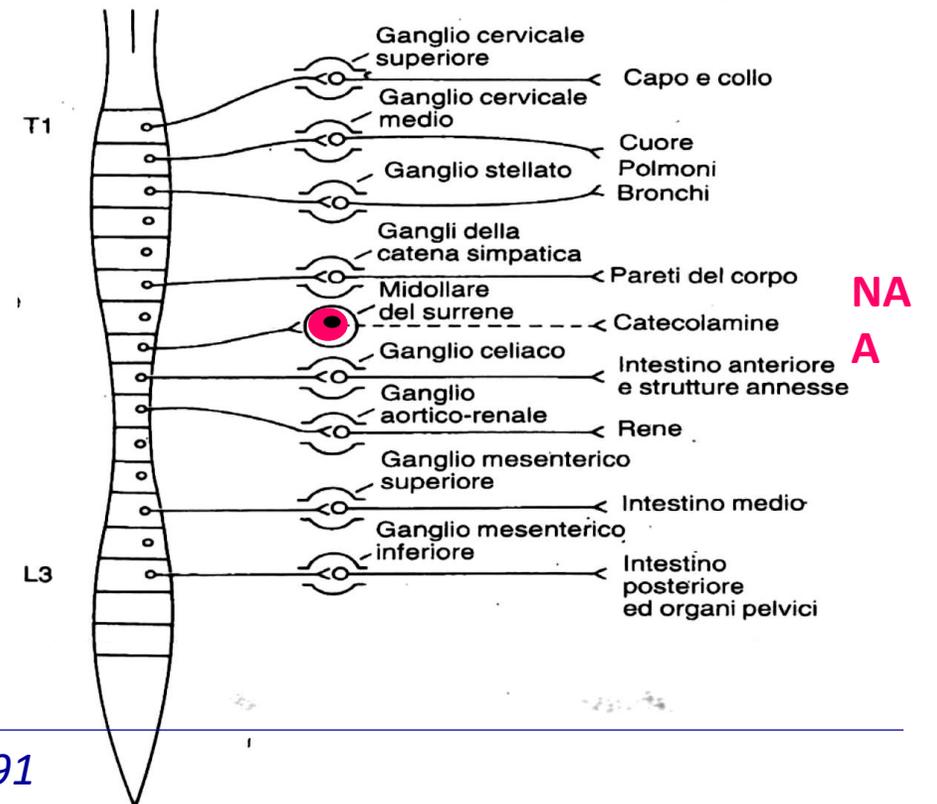
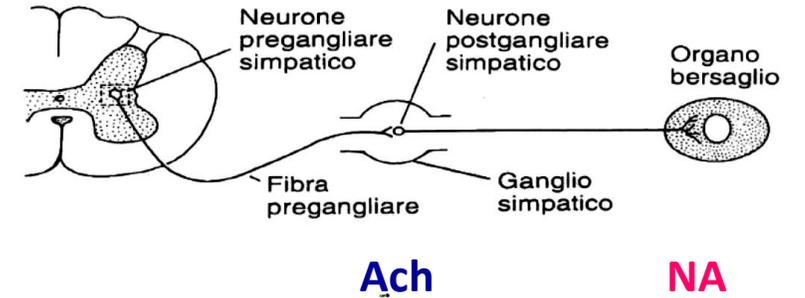
$\alpha 1$	$\alpha 2$ (pre)	$\beta 1$	$\beta 2$	D1	D2 (pre)
Costrizione vasi	Inibizione rilascio NA	Cronotropismo	Rilassamento muscolo liscio bronchi (broncodilatazione), utero, vasi del muscolo scheletrico (coronarie)	Dilatazione vasi cererali, renali, mesenterici, e coronarie	Inibizione rilascio di NA
Contrazione sfinteri (intestino-vescica)		Inotropismo	Glicogenolisi		
		Rilascio renina	Stimolo rilascio NA		
		Lipolisi ($\beta 3$)			

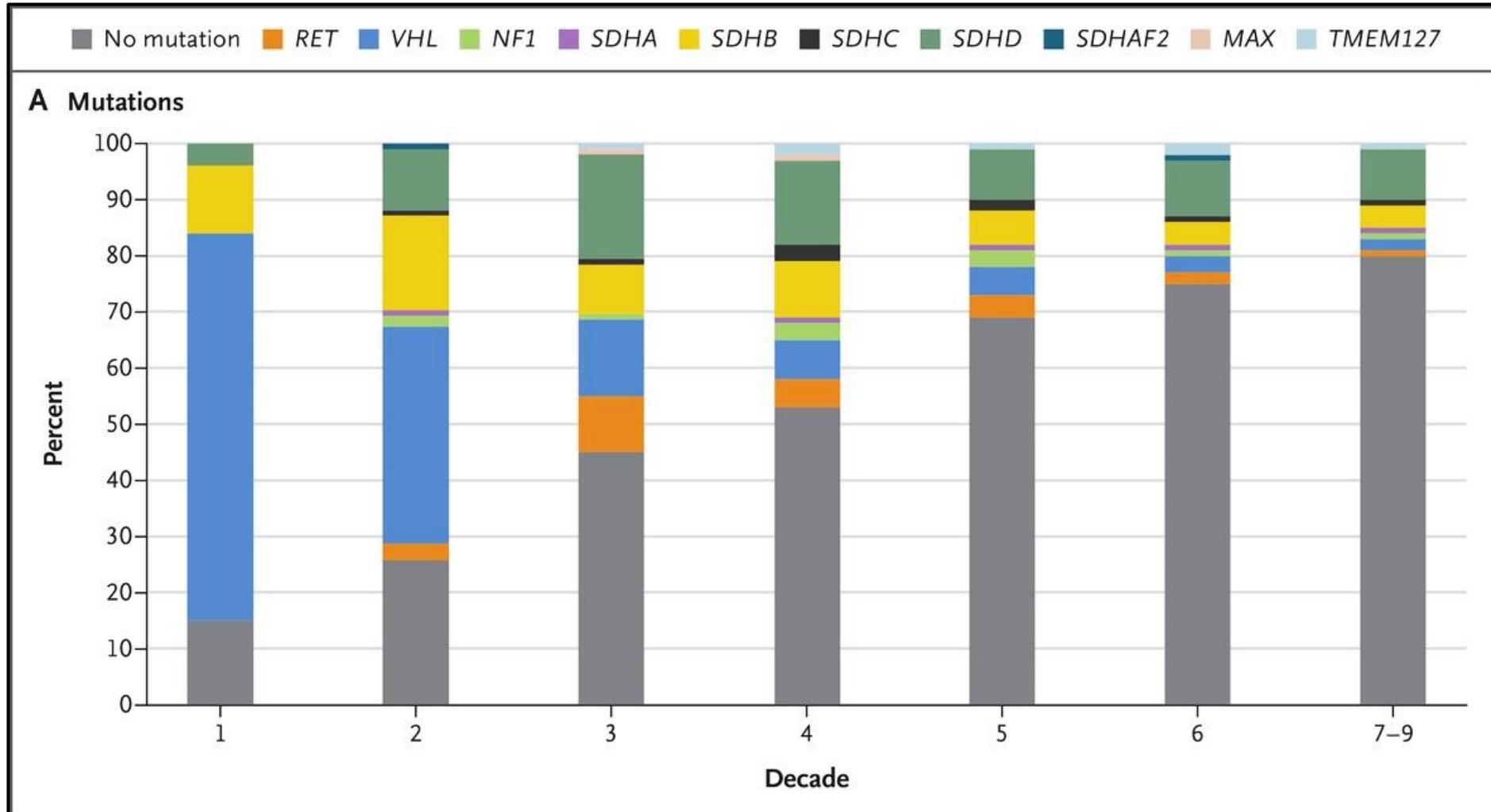


HNPGL



PPGL

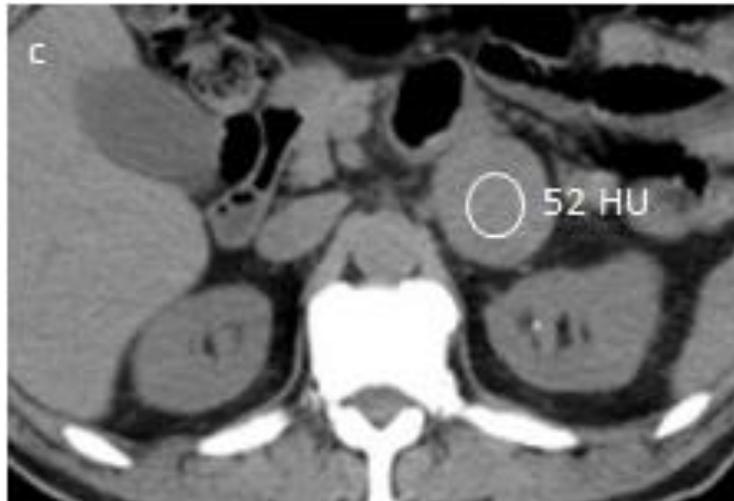




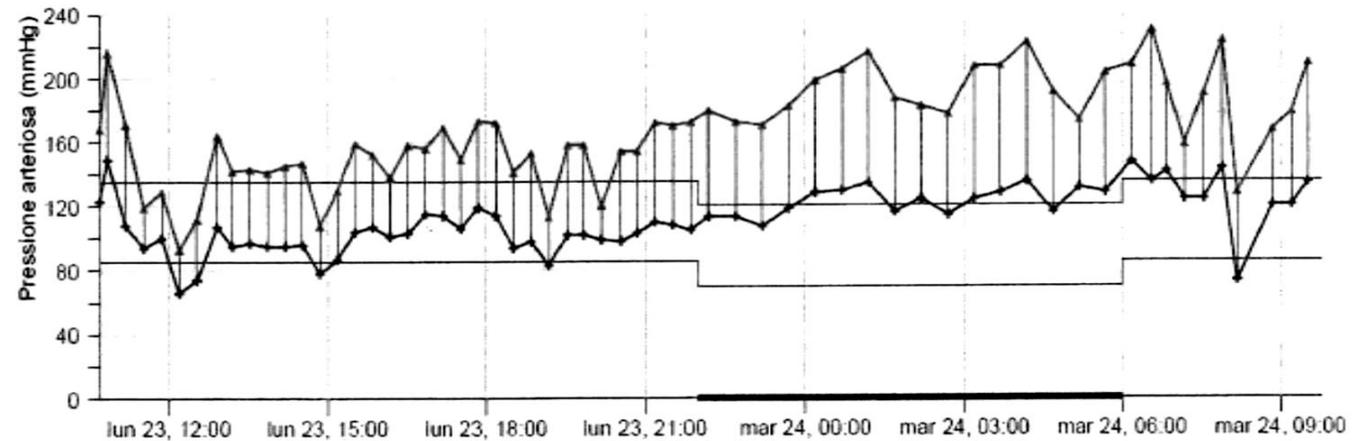
SCREENING for PPGL – who to test?

- Signs and symptoms of PPGL; spontaneous or provoked
[attenzione: PPGL è noto anche come «*the great masquerader*»]
- CVD or hypertension with signs and symptoms indicative for PPGL
- Adrenal incidentaloma with > 10 HU
- Young (<50 years) lean individuals (BMI < 25) with T2DM
- Carrier of a germline mutation in one of the PPGL susceptibility genes
- Syndromic features
- Previous history or family history of PPGL

- 62 anni M
- Dolore addominale (colecistite)

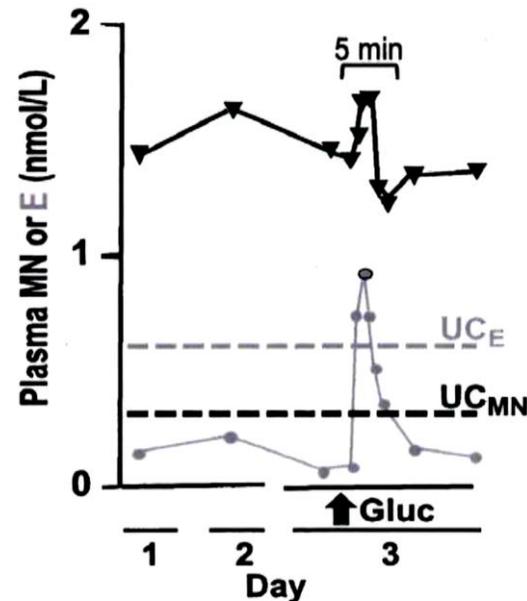


- 37 anni M
- Tachicardia sinusale 120 bpm, PA 160/100 mmHg, sudorazioni profuse



SCREENING for PPGL – which test?

Screening for PPGL should involve either measurements of **urinary fractionated or plasma free metanephrines**, with the latter undertaken in the supine position with reference intervals according to that position.



Nicotina
 Caffeina
 Amfetamina
 Metamfetamina
 Cocaina
 Efedrina
 Pseudoefedrina
 Venlafaxina/Duloxetina
 Fenossibenzamina
 Ioimbina
 Mirtazapina
 Quetiapina
 Clozapina
 Risperidone
 (Farmaci antipertensivi)

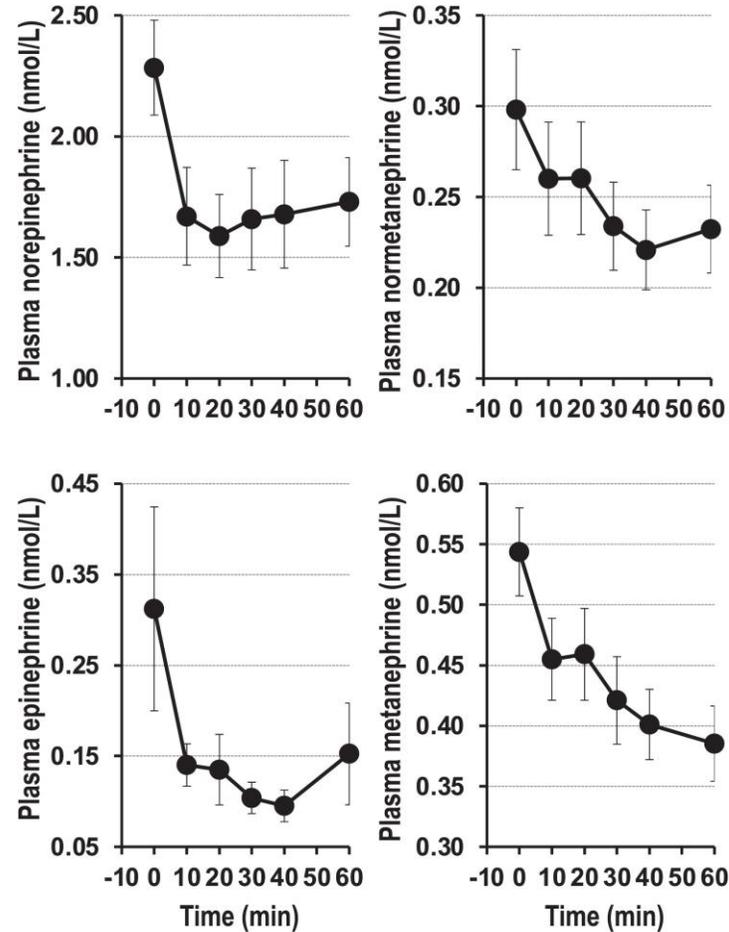
 Dieta – dopamina

 Malattie acute intercorrenti
 Intensive care unit

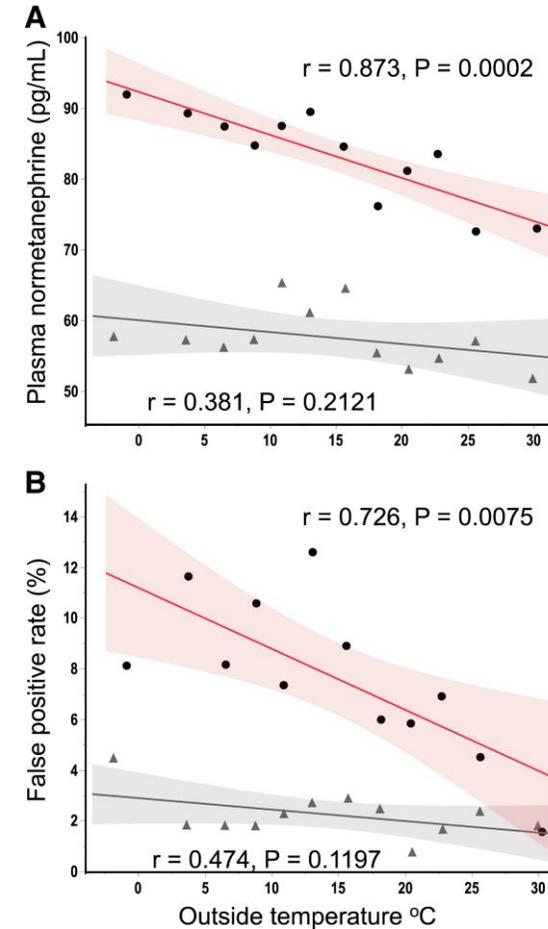
Table 7. Acute stressors associated with false-positive test results

	Acute daily stressors	Precautions
1	Physical exercise	Vigorous exercise should be avoided during 24-hour urine collections and for several hours preceding blood sampling
2	Seated or upright posture during blood sampling	Blood should be drawn after at least 20 minutes of supine rest—patients should be fully supine
3	Cold environment	Blood should be drawn after sufficient time to acclimate to warm inside temperatures
4	Acute emotional stress	
	Venipuncture	For children or adult patients with needle phobia use indwelling cannulae—urine is an alternative
	Stressful working days	24-hour collections of urine should be avoided on stressful working days

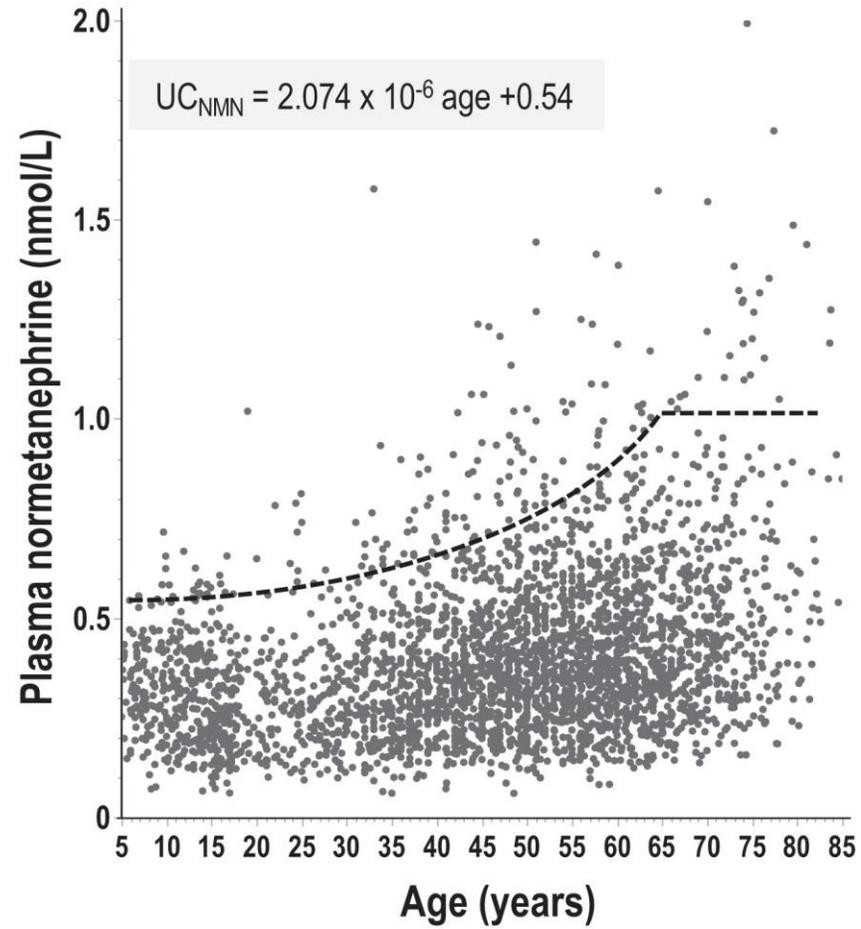
Changes in plasma concentrations of norepinephrine, normetanephrine, epinephrine, and metanephrine after transition from the seated to the supine position at time=0



Relationships of plasma concentrations (A) and rates of false-positive test results (B) for plasma normetanephrine with outside temperature



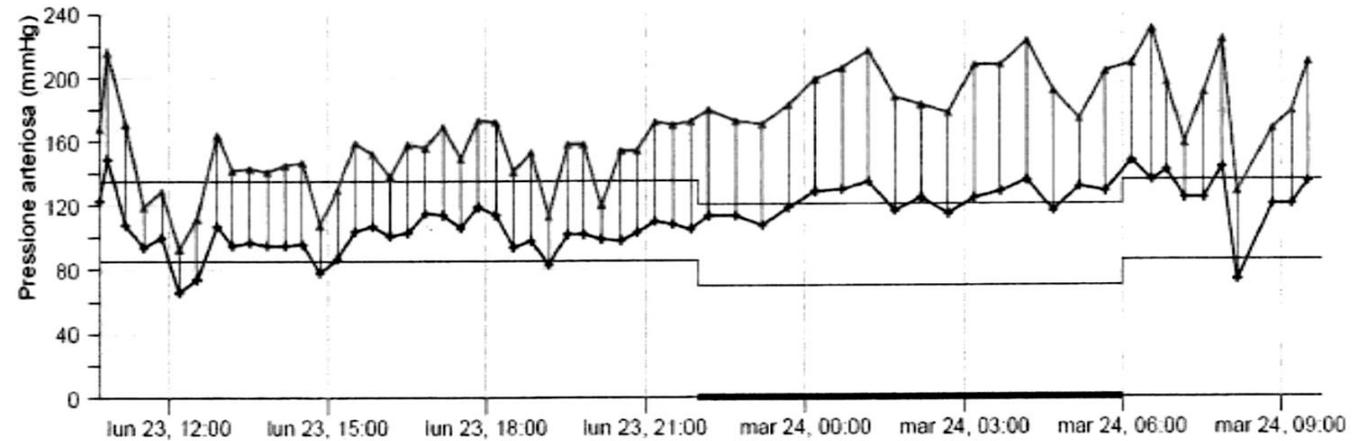
Relationship between age and plasma concentrations of normetanephrine for subjects without PPGL



- 62 anni M
- Dolore addominale (colecistite)



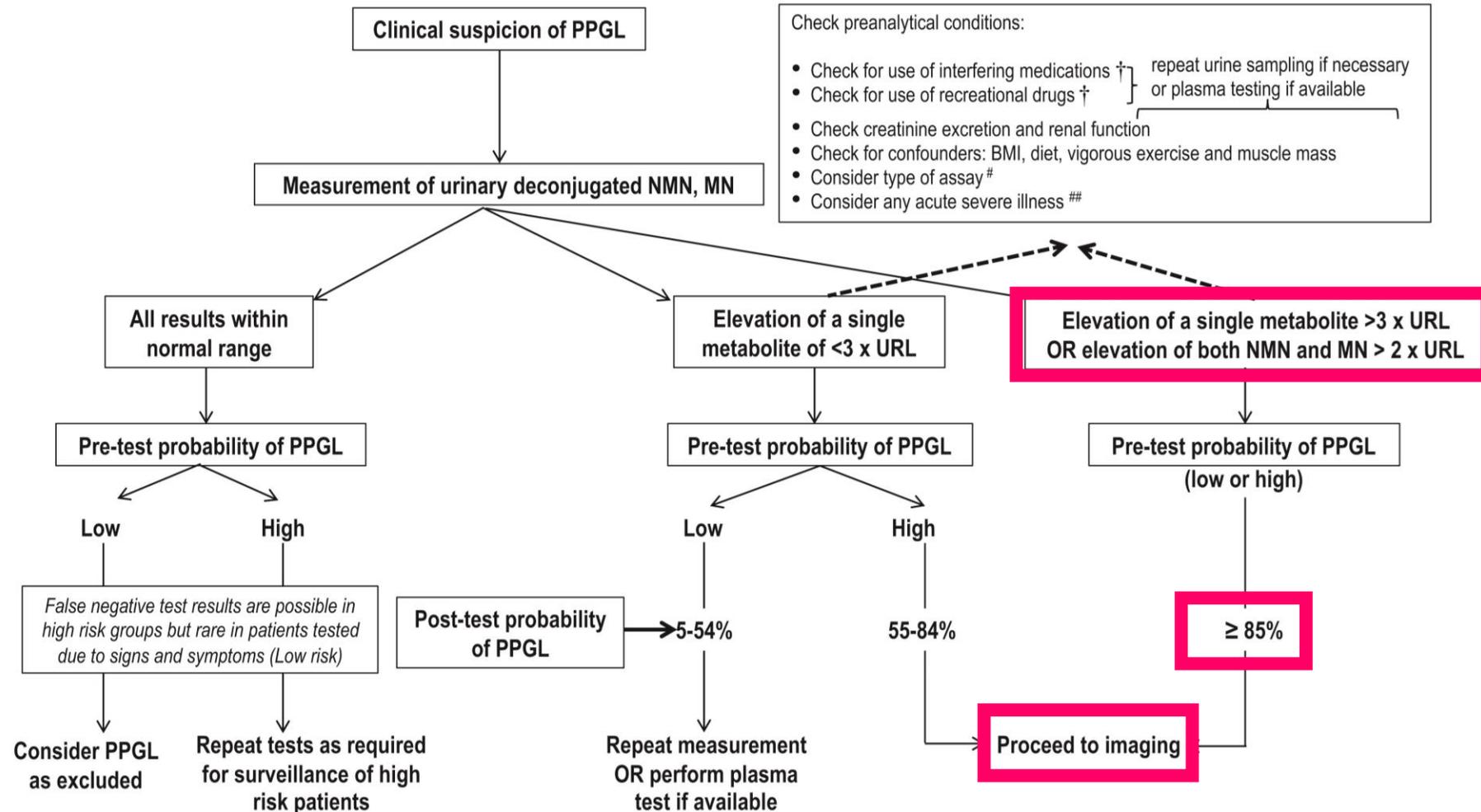
- 37 anni M
- Tachicardia sinusale 120 bpm, crisi ipertensiva, sudorazioni profuse



U-Metanefrina libera 24h **931.2** v.r. 44-261
 U-Normetanefrina libera 24h **823.2** v.r. 138-521

U-Metanefrina libera 24h 6.7 v.r. 44-261
 U-Normetanefrina libera 24h **2392.0** v.r. 138-521

INTERPRETATION of TEST RESULTS



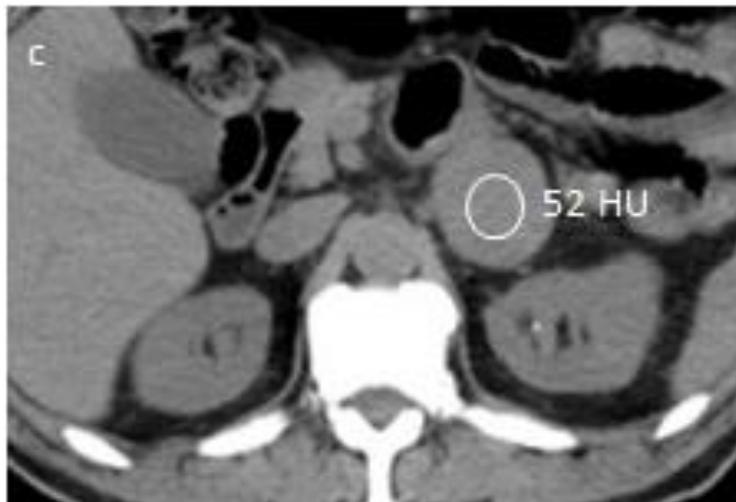
IMAGING for PPGL – which test?

Imaging studies to locate PPGL should be initiated once there is a clear biochemical evidence

Anatomic imaging by **contrast enhanced-CT or MRI** is sufficient to locate a tumor and proceed to surgery

Combined **functional imaging** allows for detection of metastases and multifocality and links with targeted radionuclide therapy

Disease	First choice
PHEO (sporadic)	[¹⁸F] FDOPA or [¹²³I]MIBG
Inherited PHEO (NF1/RET/VHL/MAX except SDHx)	[¹⁸F] FDOPA
HNPGL (sporadic)	[⁶⁸Ga] SSA
Extra-adrenal sympathetic and/or multifocal and/or metastatic and/or SDHx mutation	[⁶⁸Ga] SSA



U-Metanefrina libera 24h **931.2** v.r. 44-261
 U-Normetanefrina libera 24h **823.2** v.r. 138-521

NGS – studio geni: *FH, MAX, NF1, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL, ATRX, DNMT3A, EGLN1, EGLN2, EPAS1, FGFR1, H3F3A, KIF1B, KMT2D, MDHS, MEN1, MERTK, MET, SDHAF1, SDHAF3, SDHAF4, SLC25A11, TP53* con esito **negativo per mutazioni**



[¹⁸F] FDOPA o [¹²³I] MIBG

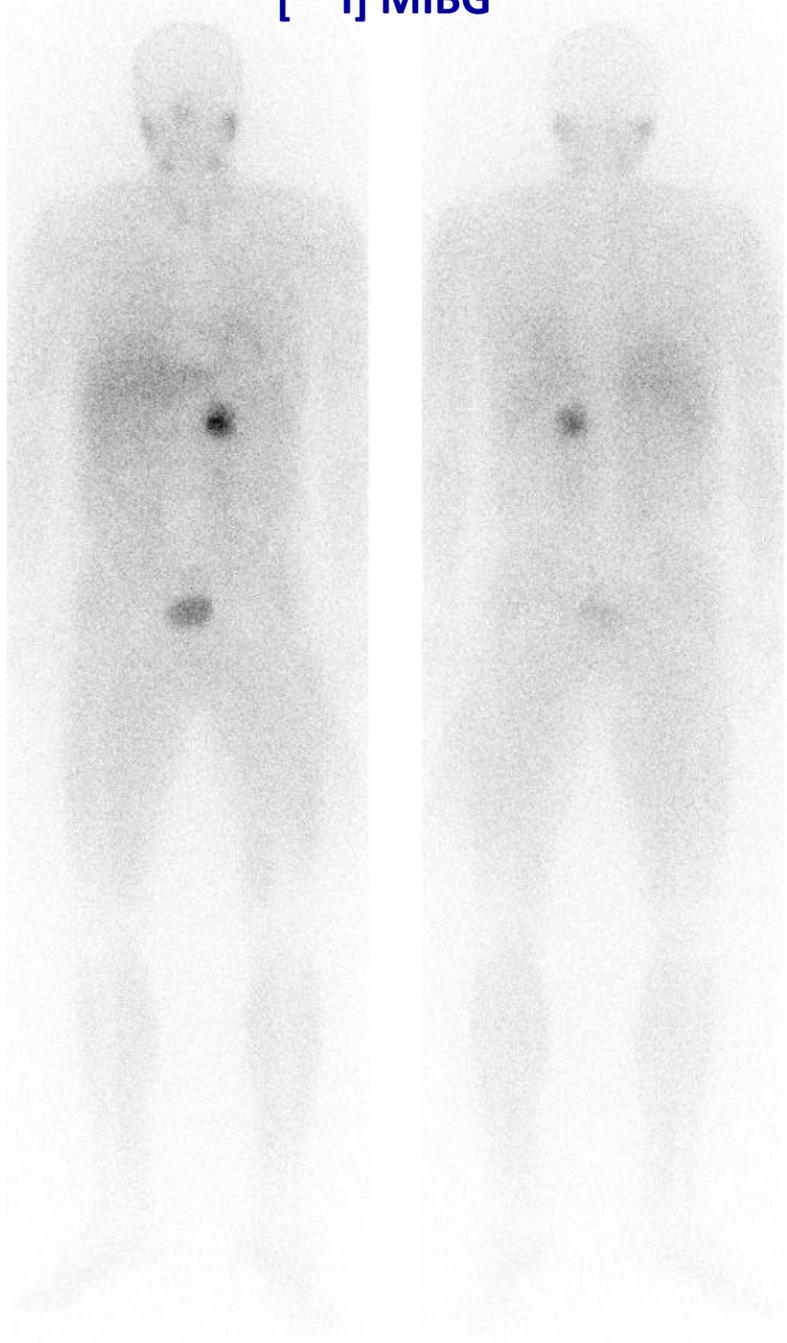
U-Metanefrina libera 24h 6.7 v.r. 44-261
 U-Normetanefrina libera 24h **2392.0** v.r. 138-521

NGS – studio geni: *FH, MAX, NF1, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL, ATRX, DNMT3A, EGLN1, EGLN2, EPAS1, FGFR1, H3F3A, KIF1B, KMT2D, MDHS, MEN1, MERTK, MET, SDHAF1, SDHAF3, SDHAF4, SLC25A11, TP53* con esito **presenza variante c.314T>A del gene SDHB**

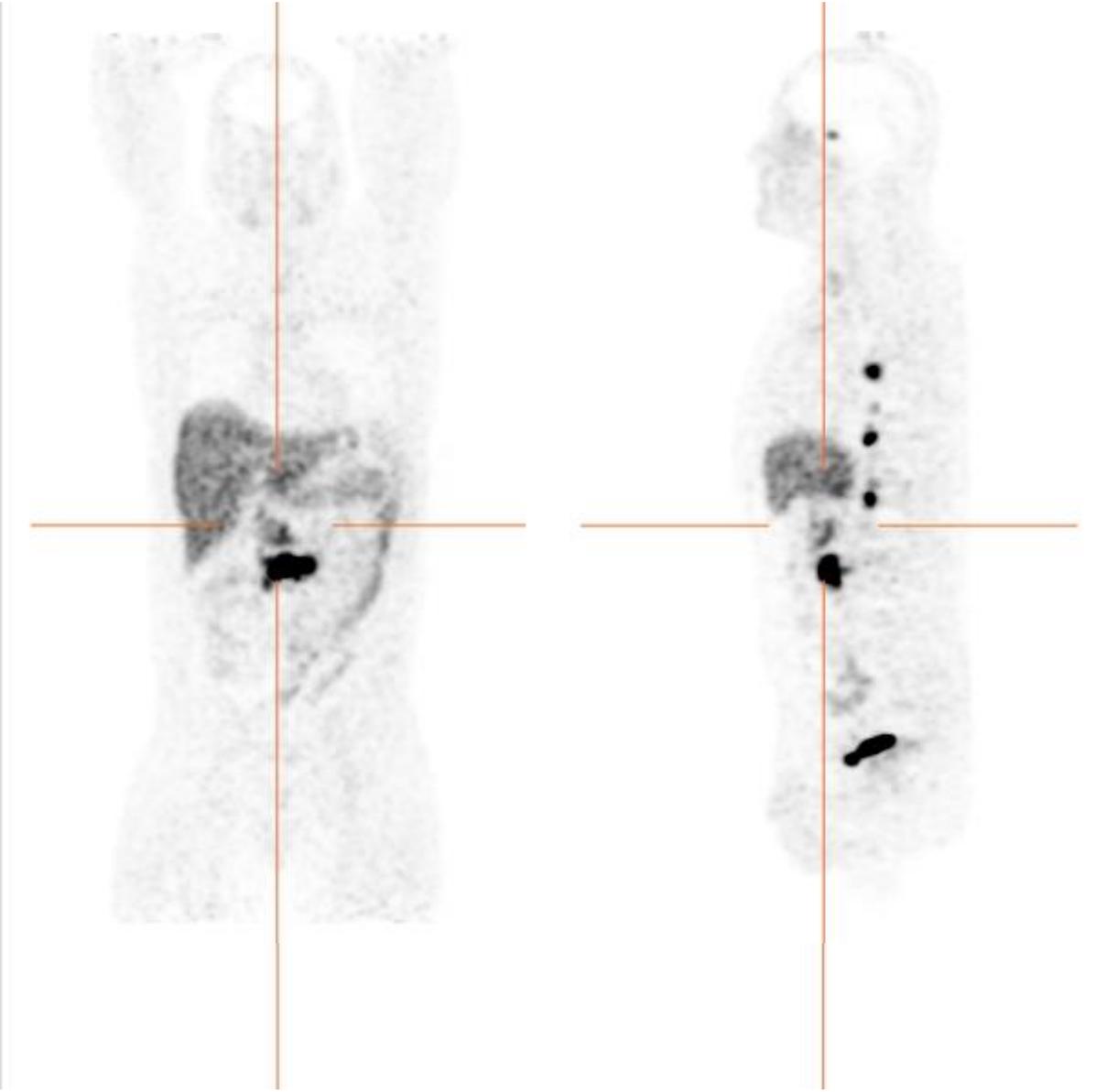


[⁶⁸Ga] SSA

[¹²³I] MIBG



[⁶⁸Ga] SSA



Caso 1 **Feocromocitoma sporadico**

U-Metanefrina libera 24 h >3x

Wild-type

Massa surrenalica 55mm 53 HU

Scintigrafia non altre localizzazioni

Terapia α -litica 7-14 giorni

Surrenectomia (attenzione a manipolazione!)

Istologico: feocromocitoma

Follow-up biochimico annuale (per 10 anni)

Caso 2 **Paraganglioma metastatico**

U-Normetanefrina libera 24 h >5x

Variante c.314T>A del gene SDHB

Massa extrasurrenalica di 56x76 mm

PET TC Gallio captazione retroperitoneale a livello massa indicata in TC e in stazioni sovradiafammatiche mediastiniche, di cui la maggiore di 3 cm

Terapia α -litica 7-14 giorni

Debulking

Istologico compatibile con paraganglioma

Sunitinib off label

Attende PRRT off label-

Caso 2

Variante c.314T>A del gene SDHB

Ricerca mutazione figli dopo l'età di 5 anni

TAKE HOME MESSAGES

Lenders JWM et al. J Clin Endocrinol Metab 2014; 99:1915-1942

Taieb D et al. Eur J Nucl Med Mol Imaging 2019;46:2112-2137

Lenders JWM et al. J Hypertens 2020; 38:1443-1456

Neumann HPH et al. N Engl J Med 2019;381:552-65

Eisehnofer G et al. Endocr Rev 2023; 44(5):862-909

Darr R et al. Clin Endocrinol (Oxf) 2014; 80 (4):478-486

Pommer G et al. J Clin Endocrinol Metab 2022; 107(9):e3689-e3698

PRESENTAZIONE (1)

- Sig.ra Tania S., 63 anni
 - APP: Ipertensione arteriosa di nuovo riscontro (**improvviso rialzo valori pressori in paziente precedentemente normoteso**)
 - APR: diagnosi recente di T2DM.
 - EO: PA 160/95 mmHg, FC 90 bpm. Normopeso.
-

PRESENTAZIONE (2)

ESAMI PRIMA del RICOVERO		
Parameter	Value	Reference range
Glucose	139	65-110 mg/dL
Glucose	136	65-110 mg/dL
Creatinine	1.25	65-110 mg/dL
Na+	139	135-145 mEq/L
K+	4.37	3.5-5 mEq/L
HbA1c	6.6%	4.3-5.9 %
AER	0.008	<0.030
Insulin	4.9	2-25 uUI/mL
C-peptide	2.1	0.8-4.1 ng/mL
Anti GAD	1.6	<5.0 UI/mL
ACTH	16.9	4.2-48.8 pg/mL
U-cortisol	62.1	<90 ug/24h
U-norepinefrine	1355.7	15-80 ug/24h
U-epinefrine	257	<15 ug/24h
U-dopamine	300	80-400 ug/24h

ESAMI DOPO il RICOVERO		
Parameter	Value	Reference range
Creatinine	0.82	0.51-1.17 mg/dL
Na+	141	135-145 mEq/L
K+	3.80	3.5-5 mEq/L
ACTH	25.6	4.2-48.8 pg/mL
Cortisol	266.5	50-250 ng/mL
U-norepinefrine	1312	15-80 ug/24h
U-epinefrine	496.1	<15 ug/24h
U-dopamine	324	80-400 ug/24h



sospetto clinico di ...

FEOCROMOCITOMA

PARAGANGLIOMI (PPGLs)

Come diagnosticarlo?

TABLE 343-2 Biochemical and Imaging Methods Used for Pheochromocytoma and Paraganglioma Diagnosis

Diagnostic Method	Sensitivity	Specificity
24-h urinary tests		
Vanillylmandelic acid	++	++++
Catecholamines	+++	+++
Fractionated metanephrines	++++	++
Total metanephrines	+++	++++
Plasma tests		
Catecholamines	+++	++
Free metanephrines	++++	+++
CT	++++	+++
MRI	++++	+++
MIBG scintigraphy	+++	++++
Somatostatin receptor scintigraphy*	++	++
Dopa (dopamine) PET	+++	++++

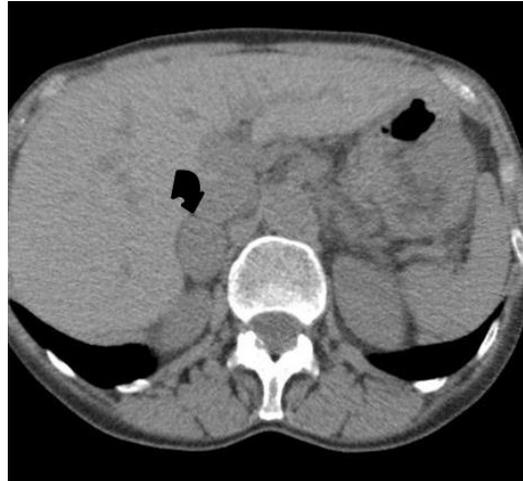
*Particularly high in head and neck paragangliomas.

Abbreviations: MIBG, metaiodobenzylguanidine; PET, positron emission tomography.

TAC e RMN ADDOME

TAC addome

- Formazione ovale al surrene di destra
- 3 cm x 2 cm x 3.5 cm
- Elevata densità

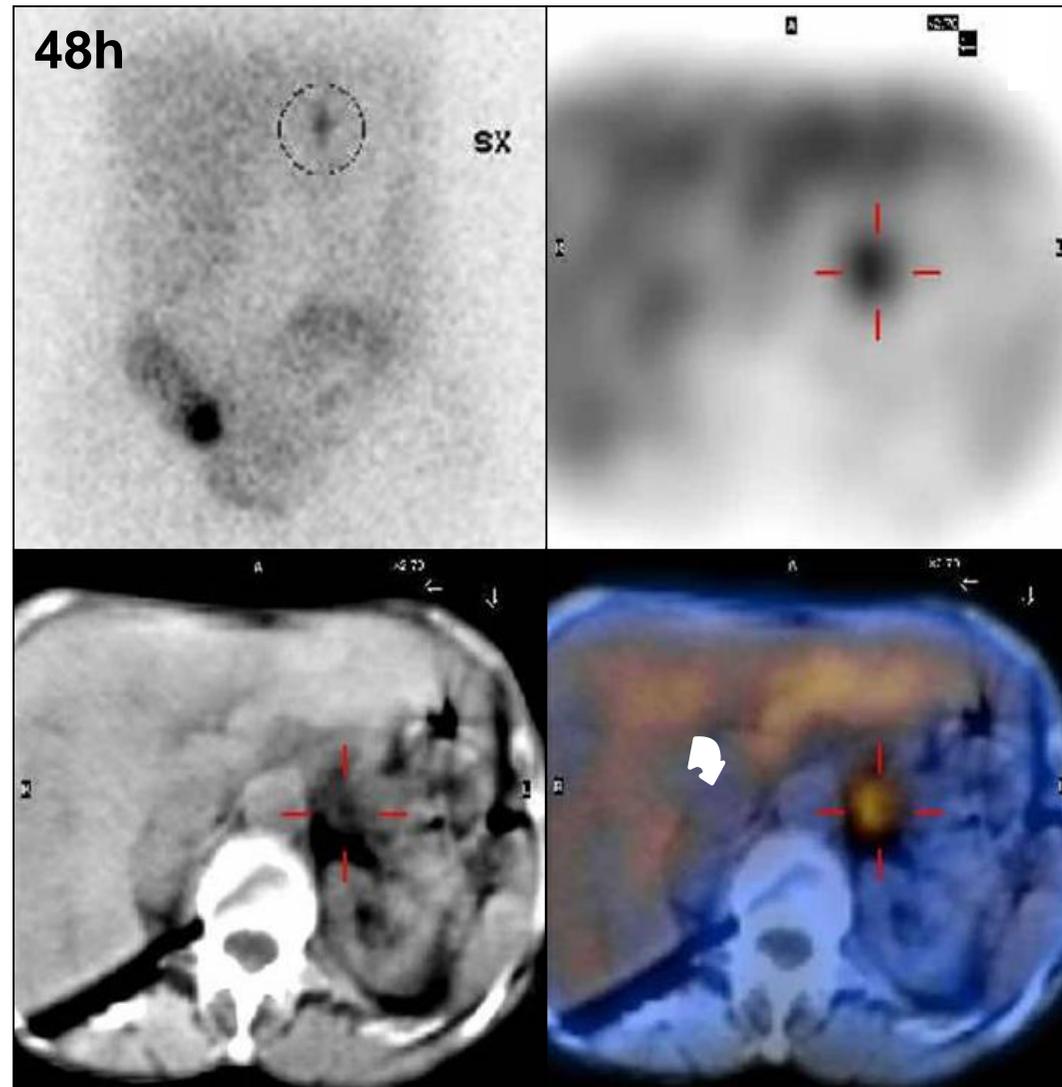


RMN addome

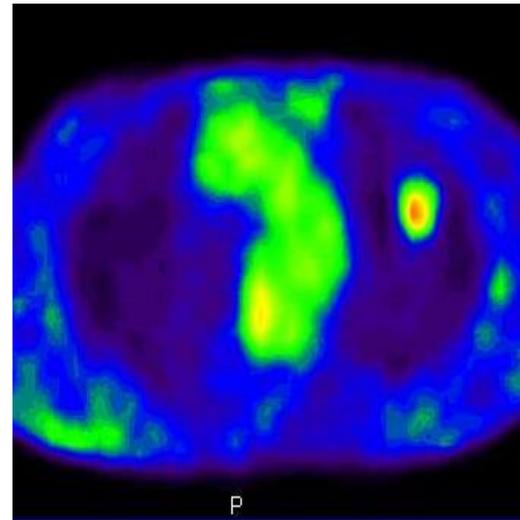
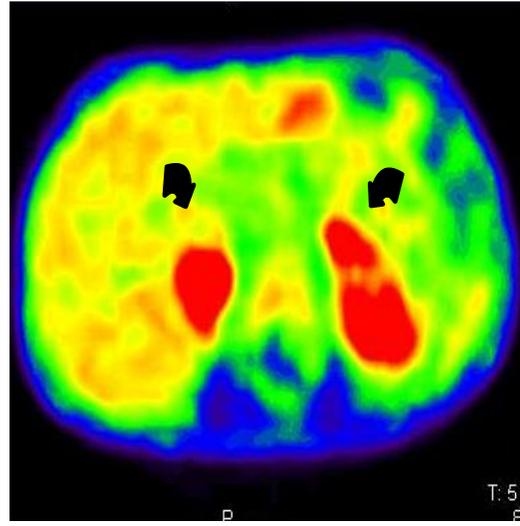
- Aspetto isointenso rispetto al fegato nelle immagini T2 pesate
- No perdita di segnale nelle immagini ad opposizione di fase



SCINTIGRAFIA ^{123}I MIBG



^{18}F FDG PET (tomografia ad emissione positroni)





quale diagnosi?

PARAGANGLIOMI (PPGLs)

feocromocitoma maligno?

- **10%** feocromocitomi è **maligno**
- diagnosi si basa sulla presenza di **metastasi (polmone, osso, fegato)**
- Esami diagnostici includono **scintigrafia con ^{123}I -MIBG e PET/TAC con ^{18}F -FDG (o Gallio)**
- terapia prevede comunque **intervento chirurgico + chemioterapia o terapia radiometabolica PRRT**

ESAMI PREOPERATORI

"All patients with an adrenal mass and biochemical evidence of pheochromocytoma should undergo surgery"
(Grumbach MM Ann Intern Med 2003)

Parameter	Value	Reference range
pH	7.5	7.38-7.43
HCO ₃ ⁻	49	25 mmol/L
K ⁺	2.3	3.5-5 mEq/L
ACTH	326	4.2-48.8 pg/mL
Cortisol	2489	50-250 ng/mL
U-cortisol	>1000	<90 ug/24h

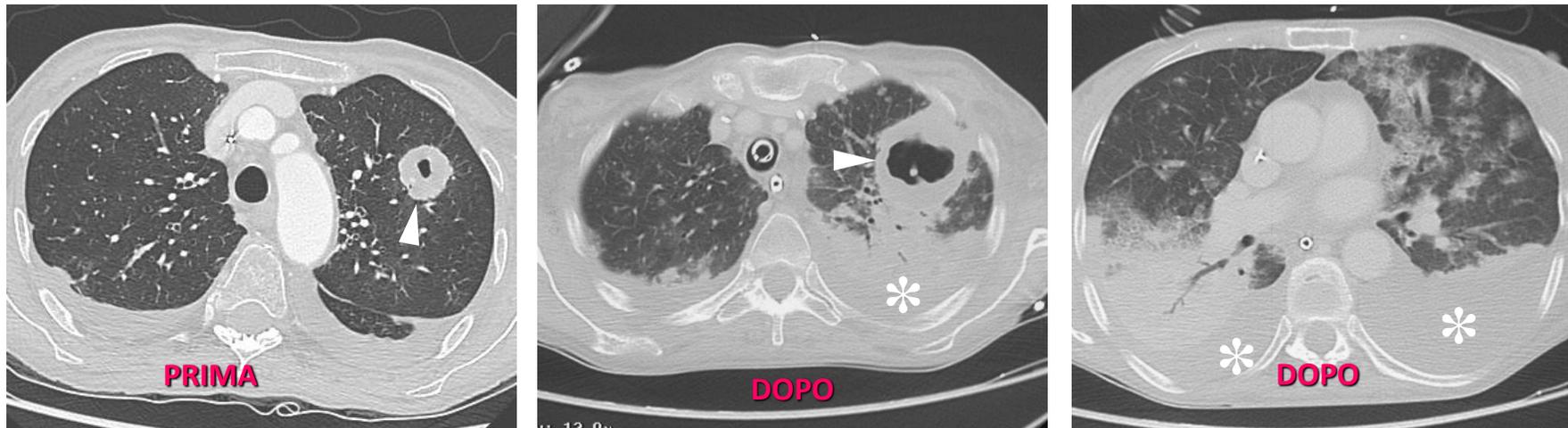
Test di soppressione con desametasone, CRH test, e RMN cerebrale escludono cause centrali di ipercortisolismo

ECTOPIC ACTH CUSHING SYNDROME (EACS)
Verosimile feocromocitoma maligno con
sindrome paraneoplastica causa di EACS

SURRENALECTOMIA

SORPRESE nel POSTOPERATORIO

1. **Sviluppo di SIRS** 2 settimane dopo l'intervento la paziente sviluppa una sindrome da infiammazione sistemica. I parametri respiratori peggiorano (a fronte di catecolamine normali), sono presenti leucocitosi ($GB\ 13.44 \times 10^3/\mu L$) e rialzo indici di flogosi (PCR 85.74 mg/L)
2. **TC torace** lesione polmonare marcatamente ingrandita con associate aree di consolidazione polmonare e versamento bilaterale.



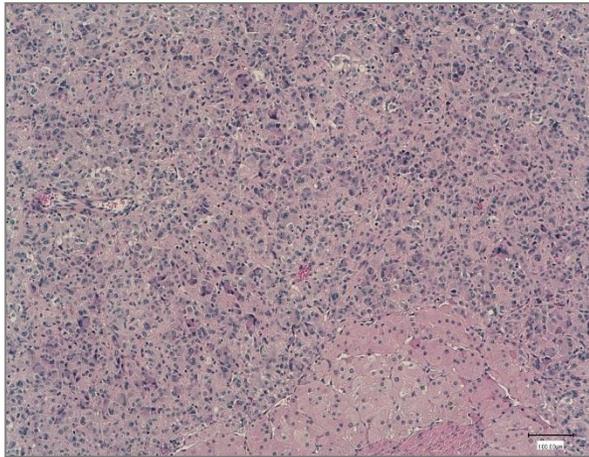
3. **Broncoscopia** non cellule atipiche.
-



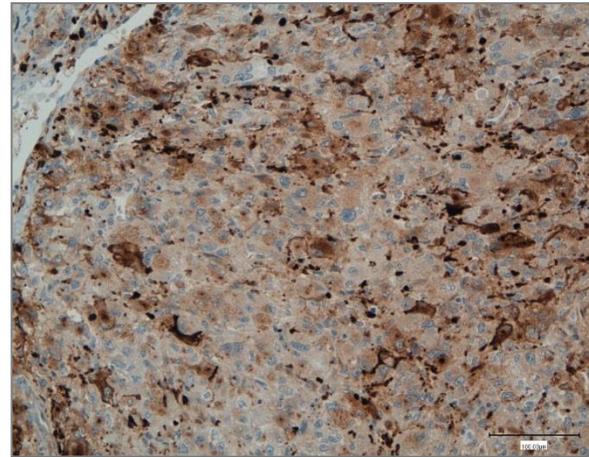
allora forse è altro ...

DIAGNOSI FINALE

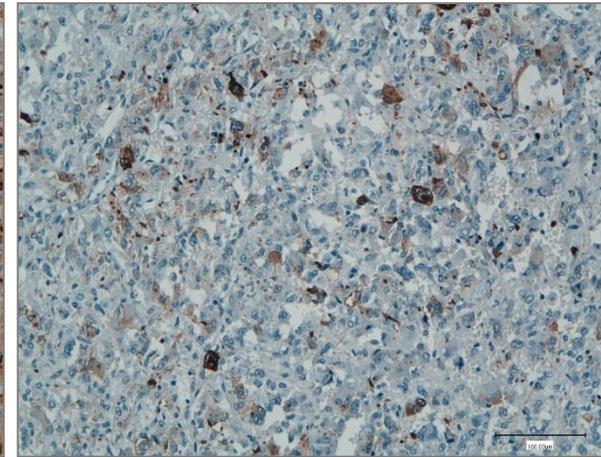
- A. Colture del LAVAGGIO BRNCOALVEOLARE POSITIVE per *Nocardia Species*. 1 emocoltura su 3 POSITIVA per *Nocardia Species*
- B. Esame istologico del pezzo operatorio ha dimostrato che ACTH era prodotto dal feocromocitoma. Dopo l'intervento i valori di ACTH e cortisolo normalizzati



E/E



Cromogranina A



ACTH

Feocromocitoma secernente ACTH con EACS complicato da nocardiosi polmonare

Conclusioni

1. Il feocromocitoma è un **great masquerader** Un versomile feocromocitoma maligno con metastasi polmonare e EACS da secrezione paraneoplastica di ACTH si è poi rivelato un feocromocitoma secernente ACTH con EACS complicato da nocardiosi polmonare
2. Il feocromocitoma è una malattia imprevedibile, rischiosa per il paziente e difficile da gestire per il medico
2. L'indagine con ^{123}I -MIBG SPECT/CT può risultare falsamente negativa nel 15% dei feocromocitomi
3. Il feocromocitoma può dare origine a una EACS intermittente
4. Nel 50% dei casi di feocromocitomi secernenti ACTH sono state segnalate infezioni opportunistiche in ragione dell'ipercorticosurrenalismo