IPERTENSIONE ARTERIOSA SECONDARIA

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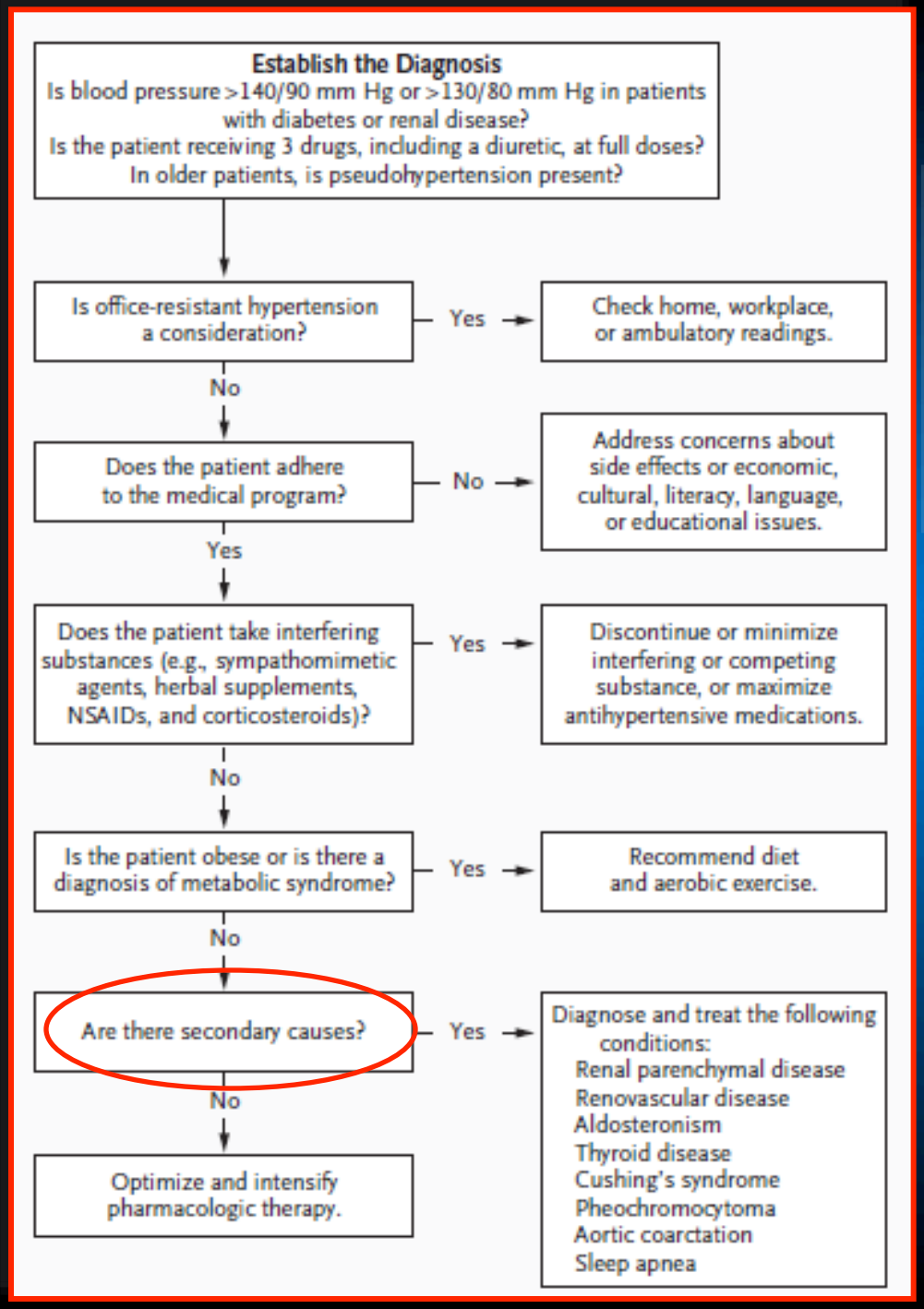
When to suspect secondary HTN?



The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Resistant or Difficult-to-Control Hypertension

Marvin Moser, M.D., and John F. Setaro, M.D.

- **Poor BP response to therapy**
- Severe elevation in BP
- Sudden onset or worsening of HTN
- OD disproportionate to the duration of HTN
- Presence of specific features

Comparsa in età pediatrica o giovanile, specie in pazienti non obesi e senza familiarità

SECONDARY HTN

	Clinical indications		
Common causes	**Clinical history**	**Physical examination**	**Laboratory investigations**
Renal parenchymal disease	History of urinary tract infection or obstruction, haematuria, analgesic abuse; family history of polycystic kidney disease.	Abdominal masses (in case of polycystic kidney disease).	Presence of protein, erythrocytes, or leucocytes in the urine, decreased GFR.
Renal artery stenosis	Fibromuscular dysplasia: early onset hypertension (especially in women). Atherosclerotic stenosis: hypertension of abrupt onset, worsening or increasingly difficult to treat; flash pulmonary oedema.	Abdominal bruit	Difference of >1.5 cm in length between the two kidneys (renal ultrasound), rapid deterioration in renal function (spontaneous or in response to RAA blockers).
Primary aldosteronism	Muscle weakness; family history of early onset hypertension and cerebrovascular events at age <40 years.	Arrhythmias (in case of severe hypokalaemia).	Hypokalaemia (spontaneous or diuretic-induced); incidental discovery of adrenal masses.

Ipertensione arteriosa secondaria

Progressivo incremento di frequenza (≈15-20% ??)

Maggior diffusione dei test di screening

Maggior conoscenza dei meccanismi fisiopatologici

Steroidi esogeni

Tabella 1. Principali cause di ipertensione secondaria	
Da sostanze esogene	Farmaci: contraccettivi orali, sterodi, FANS, cocaina, anfetamine, inbitori-MAO, ergotamina, eritropoietina, ciclosporina. Prodotti d'erboristeria contenenti liquirizia, sodio, estratti surrenalici, efedra, ma huang, saw palmeto,.
Renale	Nefro-vascolare: ateromasica o da displasia fibromuscolare Nefro-parenchimale:glomerulonefrite, malattia policistica, collagenopatia, idronefrosi, nefropatia diabetica
Endocrina	Ipo-ipertiroidismo Iperparatiroidismo Acromegalia Patologie surrenaliche: iperaldosteronismo, ipercortisolismo, feocromocitoma, iperplasia surrenalica congenita
Altre cause	Sindrome delle apnee notturne (OSAS), coartazione dell'aorta, ipertensione neurogena, eclampsia, policitemia,...

Ipertensione Arteriosa Endocrina
Prevalenza

Cause	% negli ipertesi	Test di screening
• **Ipotiroidismo**	**≈3%**	TSH reflex
• **Ipertiroidismo**	**≈1%**	TSH reflex
• **Iperparatiroidismo**	**≈1%**	→ Calcemia
• **Acromegalia**	**<1%**	⇢ GH / IGF-I
➢ **CAH**	**<1%**	
➢ **Iperaldosteronismo**	**10% (2 - 32%)**	→ PRA / aldosterone
➢ **S. Cushing**	**0.5 - 1%**	⇢ Test di Nugent…
➢ **Feocromocitoma**	**<1%**	⇢ Metanefrine/ catecolamine
	>10 %	

AGENDA

- IPERALDOSTERONISMO PRIMARIO
- FEOCROMOCITOMA

Conn's first patient with primary aldosteronism, 1954

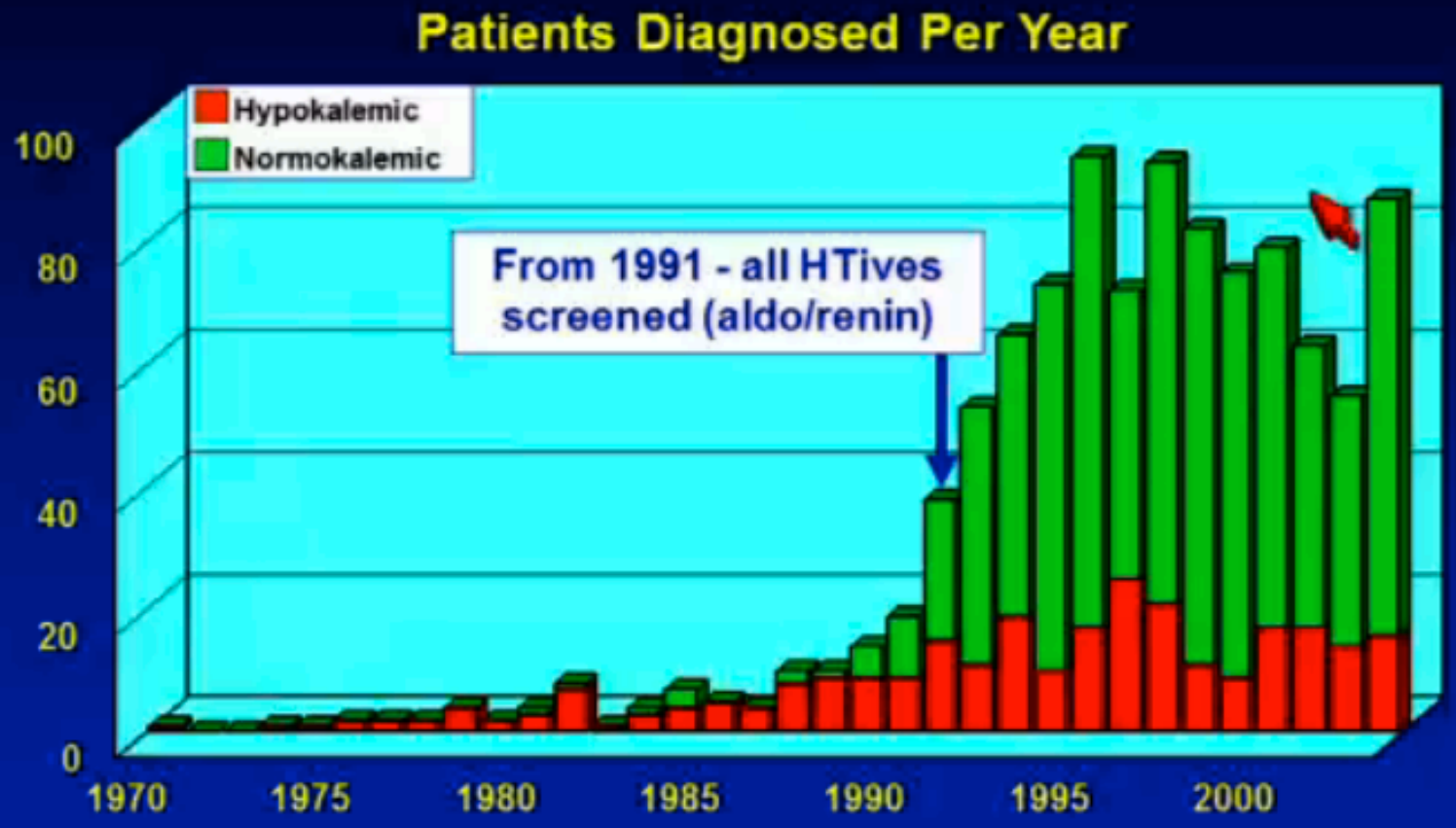
34 year old female with:

- Severe hypertension
- Severe hypokalemia, alkalosis
- Cured by removal of a 4cm aldosterone-producing adenoma situated in the right adrenal gland

Primary aldosteronism in 2013

- Common (~5-15% of pts with hypertension)
- Most patients normokalemic
- Most (approx 2/3) have bilateral PA
- Aldo excess has adverse CV and renal effects that go beyond HT
- Specific treatment against aldo excess reverses the excess in CV and renal morbidity and improves quality of life

PRIMARY ALDOSTERONISM - Greenslopes Hospital (1970-) and Princess Alexandra Hospital (2000-)



- Total number of patients with PA = >1600
- Total number undergoing ADX for unilateral PA = >400

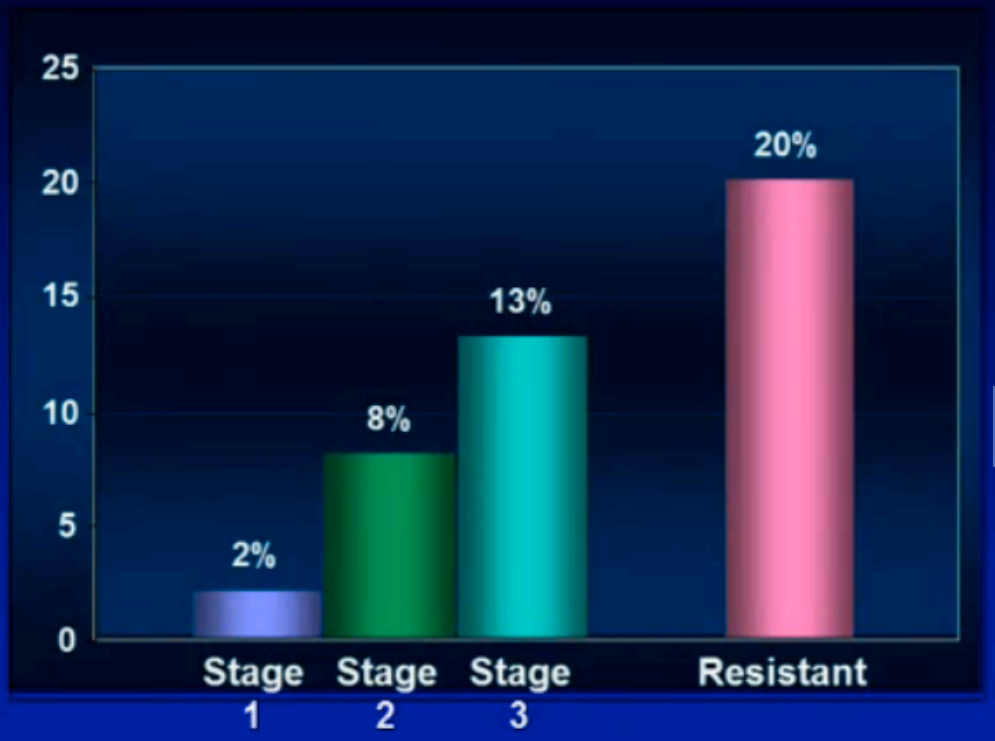
Gordon RD, et al. Lancet 1992
Stowasser M, et al. Mol Cell Endcrinol 2004

Primary Aldosteronism Subtypes

PA subtype	Frequency	Therapy
APA Angiotensin II unresponsive APA Angiotensin II responsive APA	30–50% of PA 50–70% of APA 30–50% of APA	Adrenalectomy
Unilateral adrenal hyperplasia	<5% of PA	Adrenalectomy
Aldosterone-producing carcinoma	<0.5% of PA	Adrenalectomy
Bilateral adrenal hyperplasia	50–70% of PA	Medical therapy with MRA
Familial forms		
FH-I or GRA	<1% of PA	Dexamethasone or MRA
FH-II	3–5% of PA	Adrenalectomy or MRA (as for sporadic PA)
FH-III	<1% of PA	Bilateral adrenalectomy or spironolactone

Mulatero P, Monticone S, Rainey WE, Veglio F, Williams TA, Nature Rev Endo 2013

Prevalence of PA According to Stage of HT



Mosso L, Hypertension 2003

Calhoun D, Hypertension 2002

Indicazione alla ricerca di iperaldosteronismo

2008

Clinical Practic

Table 2 Conditions that should trigger the search for primary aldosteronism in a hypertensive patient

- Hypokalemia (spontaneous or diuretic-induced)
- Resistant hypertension; grade 2 or 3 hypertension
- Early-onset (juvenile) hypertension and/or stroke (<50 years)
- First-degree relatives of patients with primary aldosteronism
- Incidentally discovered, apparently nonfunctioning adrenal mass ("incidentaloma")

2010

Curr Hypertens Rep
DOI 10.1007/s11906-010-

- Evidence of organ damage (left ventricular hypertrophy, diastolic dysfunction, AV block, carotid atherosclerosis, microalbuminuria, endothelial dysfunction), particularly if disproportionate for the severity of hypertension

Prevalen

Gian Paolo Rossi

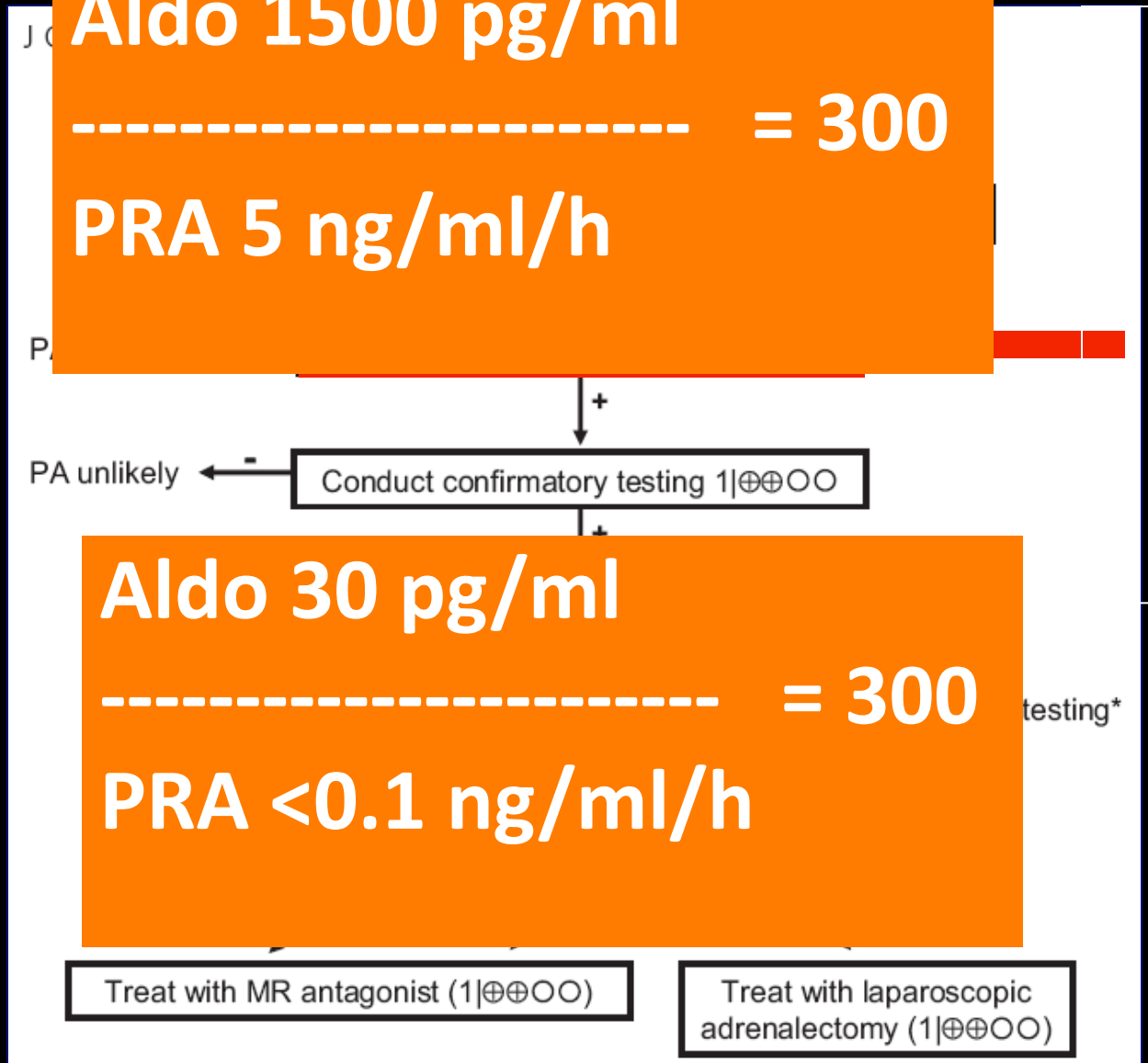
SCREENING DI MASSA?

Iperaldosteronismo

Aldo 1500 pg/ml

---------- = 300

PRA 5 ng/ml/h



Aldo 30 pg/ml

---------- = 300

PRA <0.1 ng/ml/h

FIG. 1. Algorithm for the detection, confirmation, subtype testing, and

Ratio Aldosterone / Renina

↑ = Aldo & ↓ PRA

ARR > 300

(Aldo: pg/ml & PRA: ng/ml/h)

(range 200-1000)

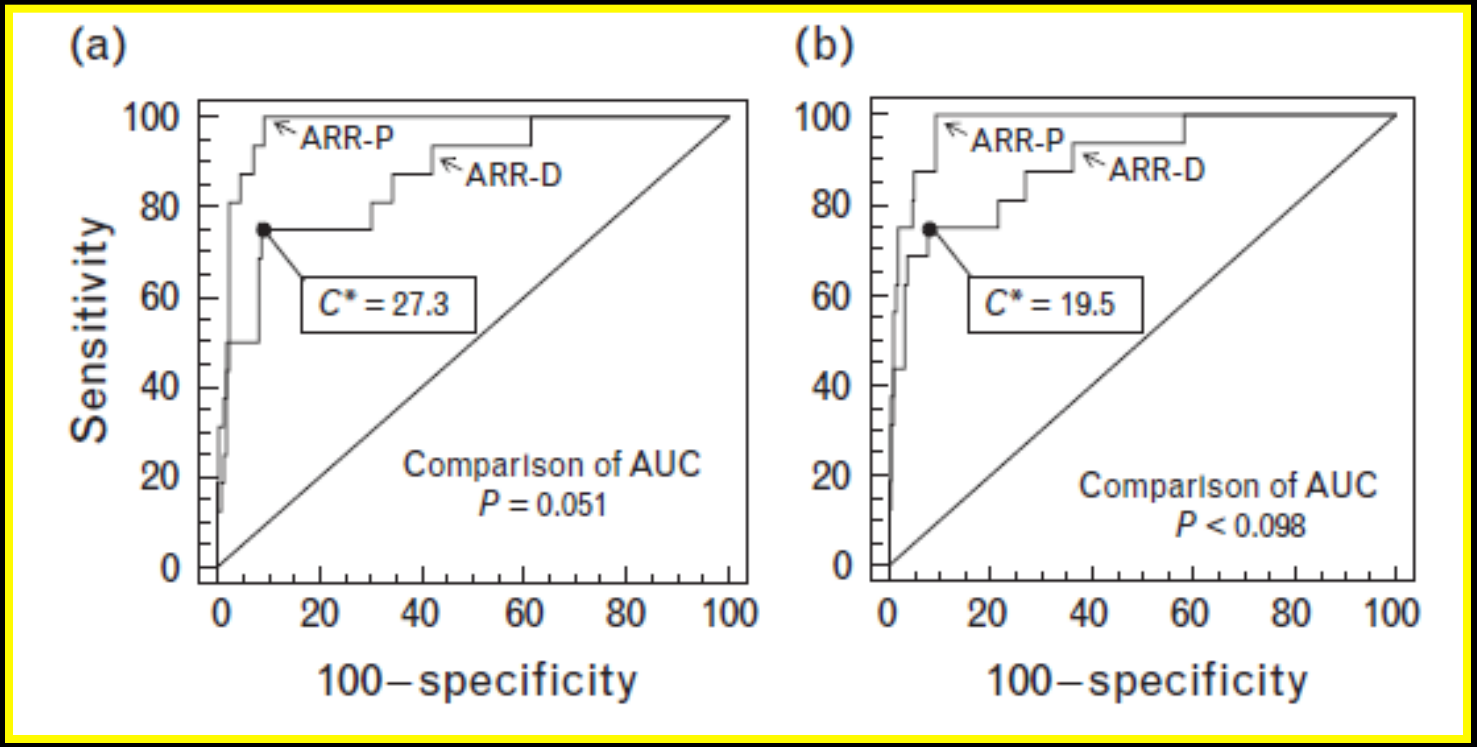
PRA < 0.2-0.3 (< 1 ng/ml/h)

Aldo > 150 pg/ml

The aldosterone–renin ratio based on the plasma renin activity and the direct renin assay for diagnosing aldosterone-producing adenoma

Gian Paolo Rossi, Marlena Barisa, Anna Belfiore, Giovambattista Desideri, Claudio Ferri, Claudio Letizia, Mauro Maccario, Alberto Morganti, Gaetana Palumbo, Anna Patalano, Elisabetta Roman, Teresa M. Seccia, Achille C. Pessina, Franco Mantero, for the PAPY study Investigators*

Journal of Hypertension 2010, 28:1892



- ✓ Il dosaggio della renina diretta è affidabile nella diagnosi di PA
- ✓ Il cut off ottimale è 27.3 ng/mU (45.3 se PAC e DRC in ng/dl)
- ✓ SE e SP sono (non significativamente) inferiori rispetto a PRA

INTERPRETAZIONE PRA

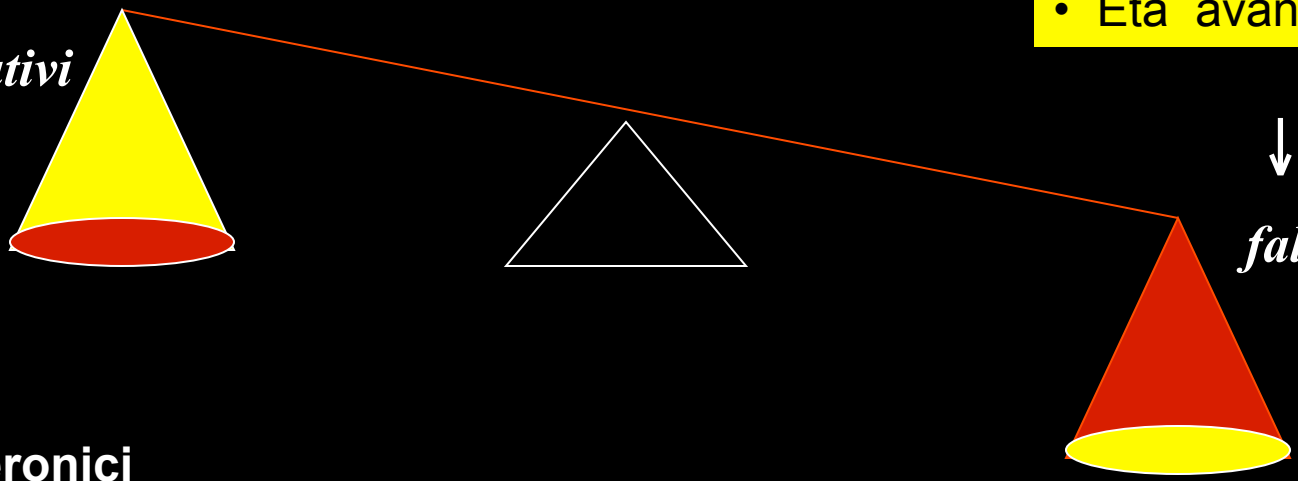
Dieta iposodica ⟷ Eccesso di sale

Sodiuria > 150 mg/24h

- Razza nera, BMI
- Età avanzata, IRC

↑ PRA

falsi negativi



↓ PRA

falsi positivi

Anti-aldosteronici

Diuretici
ACE-I, ARBs

↓ K+ : riduce la secrezione di aldosterone e può causare falsi negativi

CCB DHP

Estrogeni, Progesterone (*)

β-bloccanti
Clonidina - α metil-dopa
Inibitori della renina

FANS
Steroidi
11 β-HSD2 inibitori

SPECIAL FEATURE

Clinical Practice Guideline

Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline

John W. Funder, Robert M. Carey, Carlos Fardella, Celso E. Gomez-Sanchez, Franco Mantero, Michael Stowasser, William F. Young Jr., and Victor M. Montori*

TABLE 2. Medications that have minimal effects on plasma aldosterone levels and can be used to control hypertension during case finding and confirmatory testing for PA

Drug	Class	Usual dose	Comments
Verapamil slow-release	Non-dihydropyridine calcium channel antagonist	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table.
Hydralazine	Vasodilator	10–12.5 mg twice daily, increasing as required	Commence verapamil slow release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing, and palpitations).
Prazosin hydrochloride	α-Adrenergic blocker	0.5–1 mg two to three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension
Terazosin hydrochloride	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension

Rev Endocr Metab Disord 12: 43-48, 2011

Commentary on the Endocrine Society Practice Guidelines: Consequences of adjustment of antihypertensive medication in screening of primary aldosteronism

Evelyn Fischer · Felix Beuschlein · Martin Bidlingmaier · Martin Reincke

25 pazienti con PA	1° ARR senza modifiche terapia
25 pazienti con EH	2° ARR con modifiche secondo LG

La terapia antiipertensiva interferente è stata modificata in solo 26/50 pz. Ha effetti collaterali importanti (6 pz ospedalizzati per crisi ipertensiva, FA, scompenso). IpoK grave in 7 pz.

La variazione terapeutica ha poca influenza sulla sensibilità del test: 24/25 pz erano correttamente identificati anche con terapie interferenti nella 1ª valutazione. Molti i falsi positivi alla 1ª determinazione nei pz con EH (44%).

Variability in Aldosterone & Renin

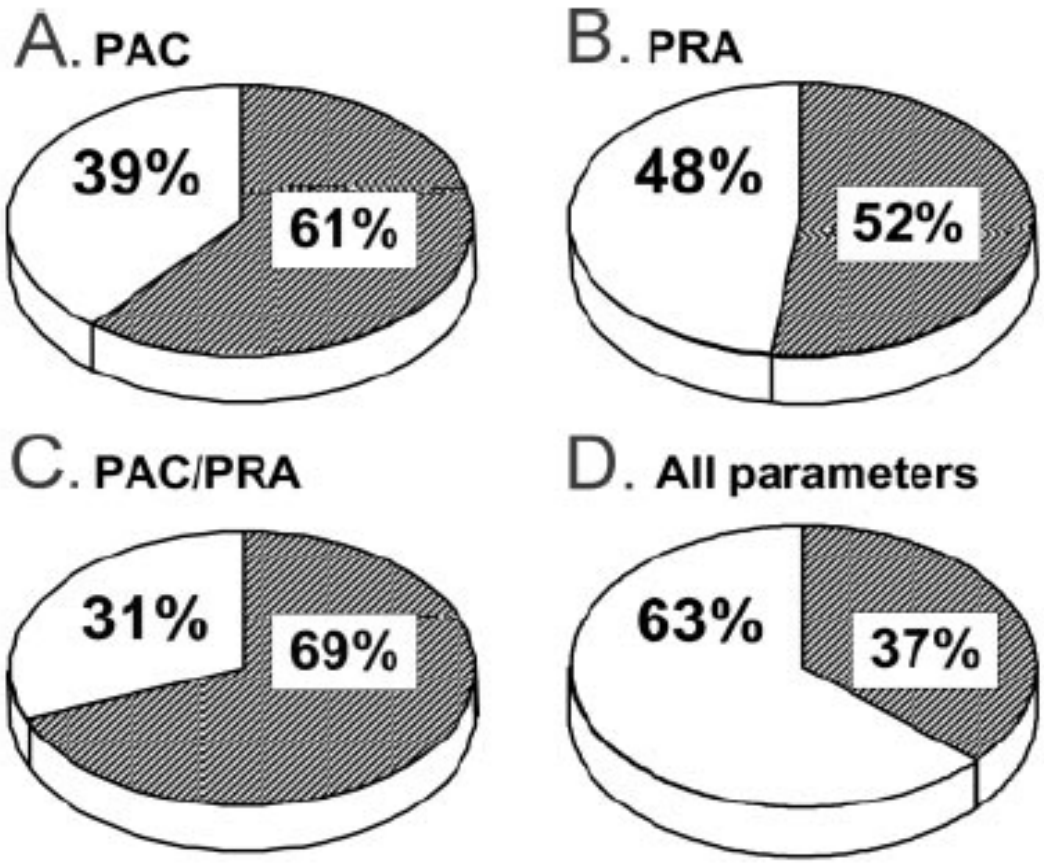


FIG. 4. Percentage of patients with consistent abnormal PAC (A), PRA (B), PAC/PRA ratio (C), and consistently abnormal all three variables (D). □, Patients without constantly typical profiles; ■, patients with constantly typical profiles.

Tanabe et al. JCEM 88: 2489–2494, 2003

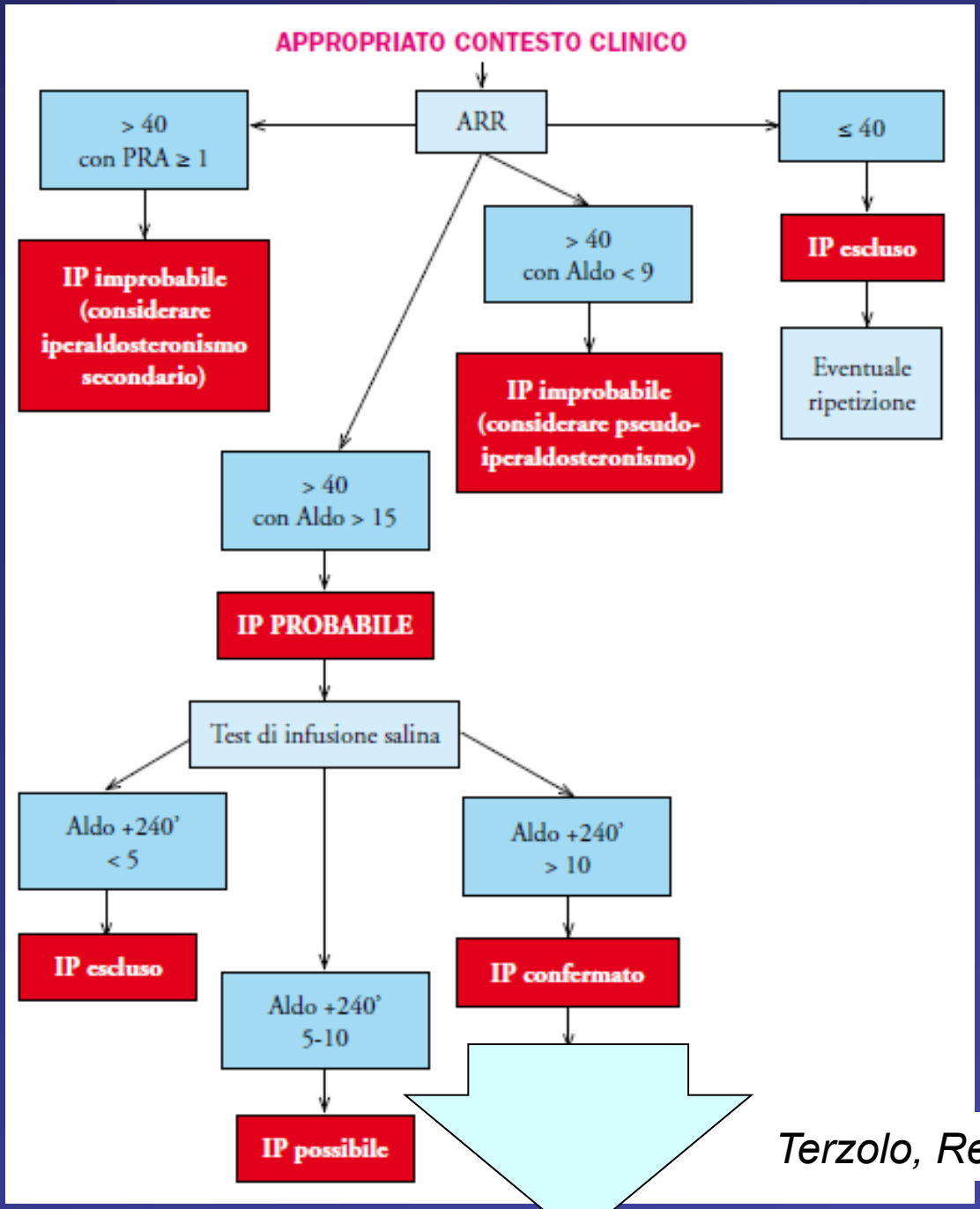
Poche regole per effettuare dosaggio di PRA e Aldosterone

- **Normalizzare il potassio**
- **Dieta normosodica** qualche giorno prima dell'esame: uNa > 150 mEq/24h
- **Sospendere diuretici -inclusi antialdosteronici- (≥ 4 settimane)**
- Sospendere betabloccanti (≥ 2 settimane)
- Sospendere altri farmaci interferenti (sostituire con Verapamil, Doxazosina)
- Prelievo al mattino dopo 1 h di ortostatismo
- Paziente seduto al momento del prelievo

In presenza di farmaci interferenti interpretare il risultato!

Ripetere valutazione di ARR

IPERALDOSTERONISMO



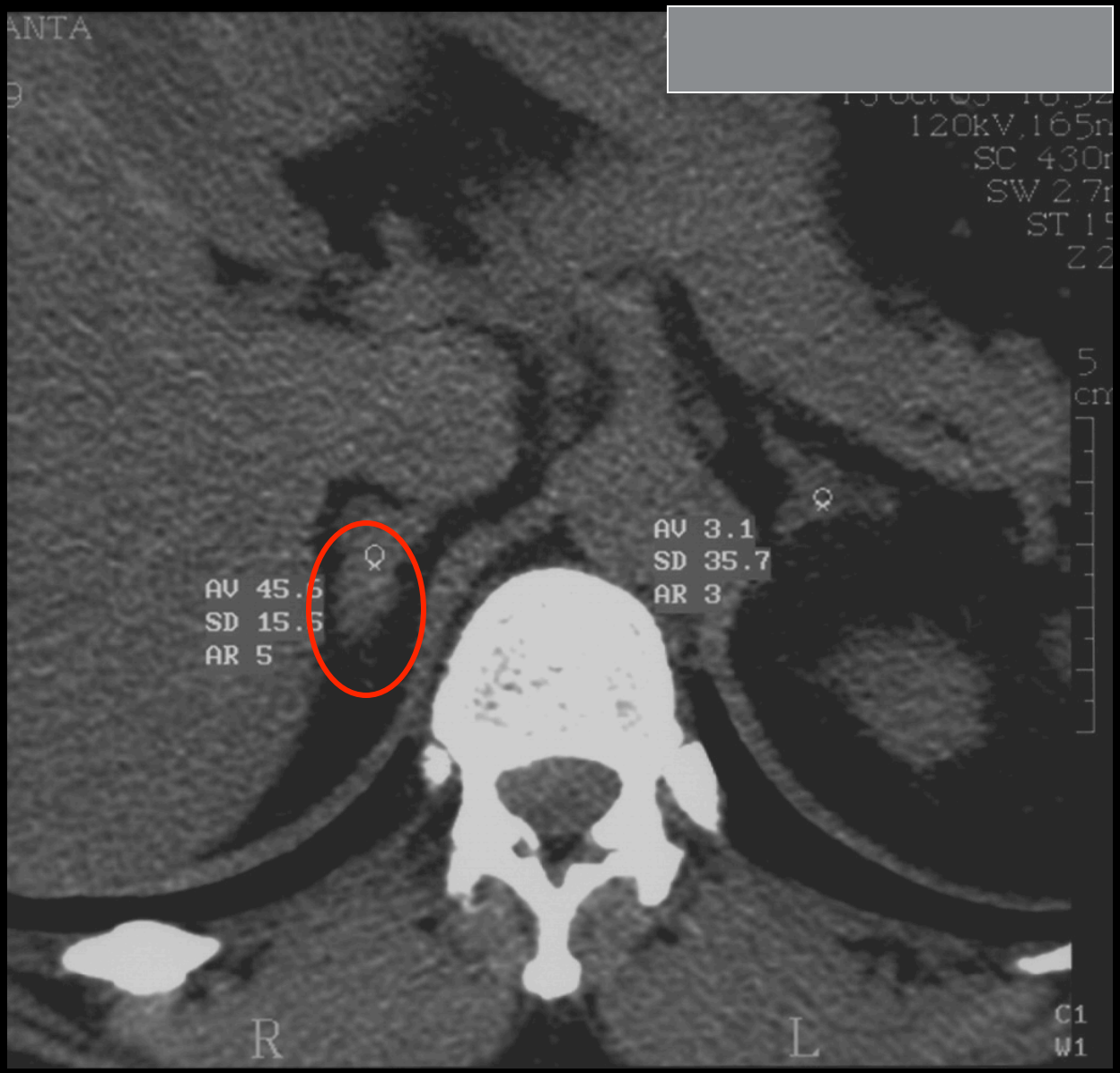
Terzolo, Reimondo, 2008

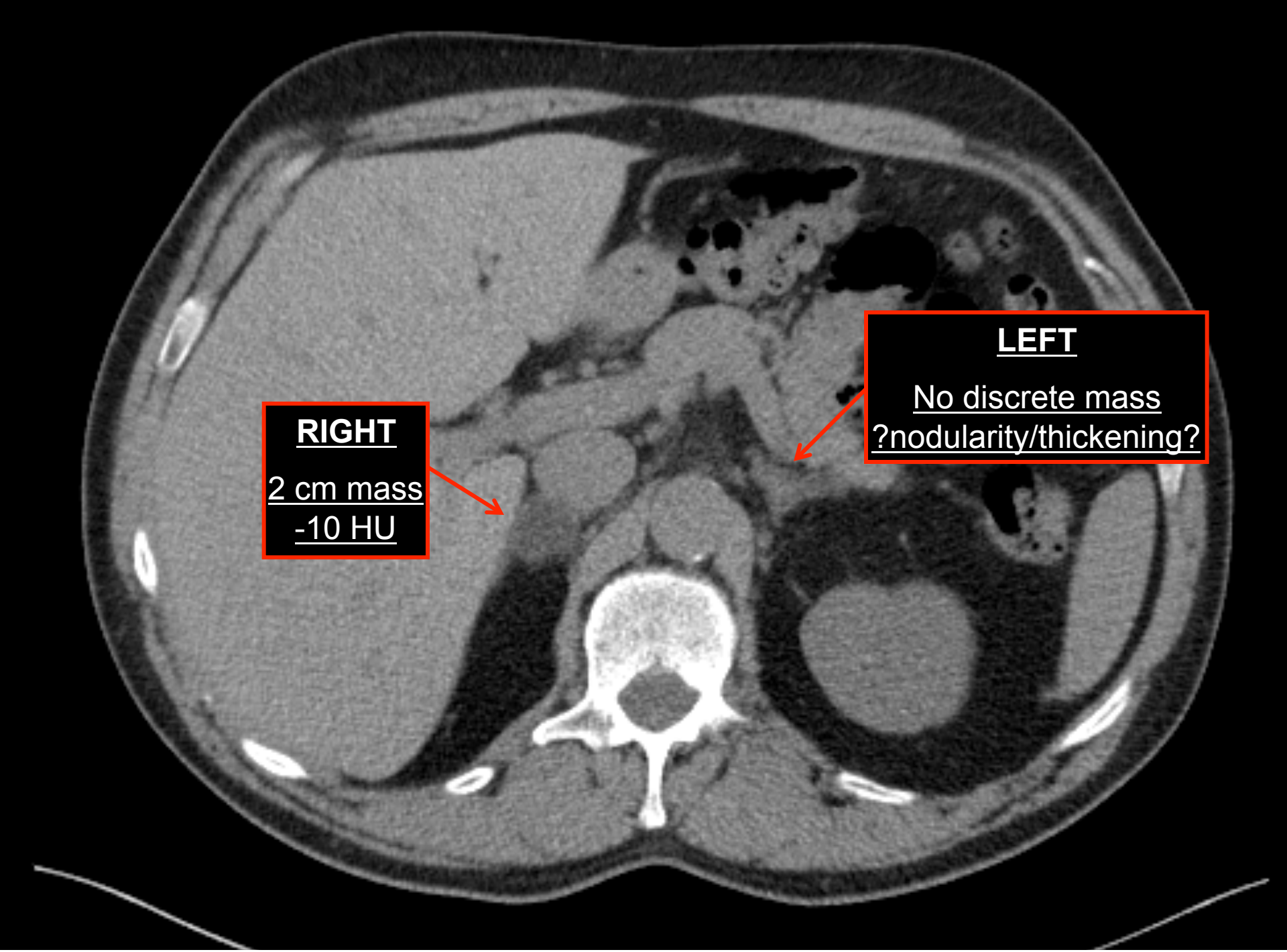
Iperaldosteronismo: sottotipi

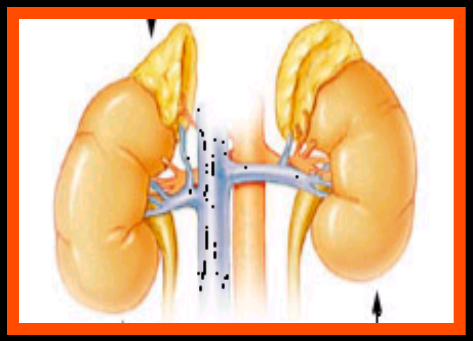
CAUSE → TERAPIA

Sottotipi	Terapia 1ª linea	Terapia 2ª linea
Unilaterale (adenoma o iperplasia)	Surrenectomia monolaterale laparoscopica	Terapia medica
Bilaterale (iperplasia)	Terapia medica	Surrenectomia mono- o bilaterale laparoscopica

Adenoma surrenalico




RIGHT
2 cm mass
-10 HU
LEFT
No discrete mass
?nodularity/thickening?



Adrenal Vein Sampling (AVS)

AVS: Gold Standard per la diagnosi di sottotipo

Definizione di gold standard di un esame:

- facilmente accessibile, alta % di successo
- sicuro
- riproducibile
- standardizzato
- sensibilità e specificità vicino a 100%
- poco costoso

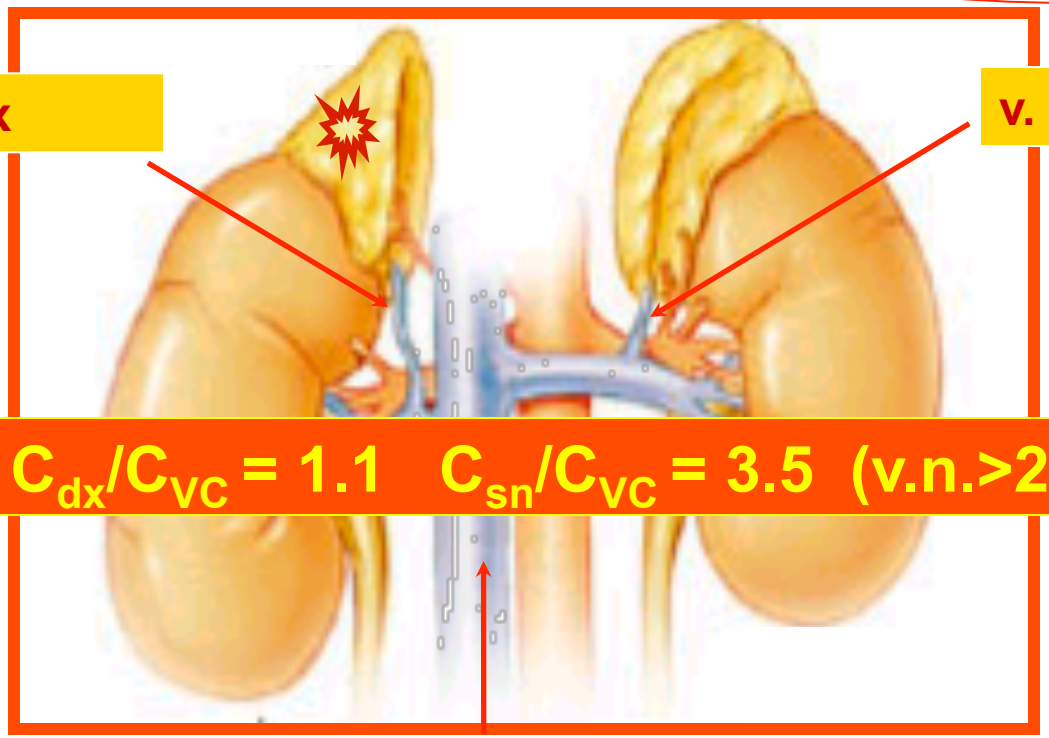
CATETERISMO VENE SURRENALICHE

Aldosterone = 41 pg/ml
Cortisolo = 6.2 μg/dl

Aldosterone =152 pg/ml
Cortisolo = 20.7 μg/dl

v. surrenalica dx

v. surrenalica sin



$C_{dx}/C_{VC} = 1.1$ $C_{sn}/C_{VC} = 3.5$ (v.n.>2)

vena cava inferiore

Aldosterone = 48 pg/ml
Cortisolo = 5.6 μg/dl

Dosaggio del cortisolo durante AVS

AVS

Aldosterone = 206 pg/ml
Cortisol = 12.6 µg/dl

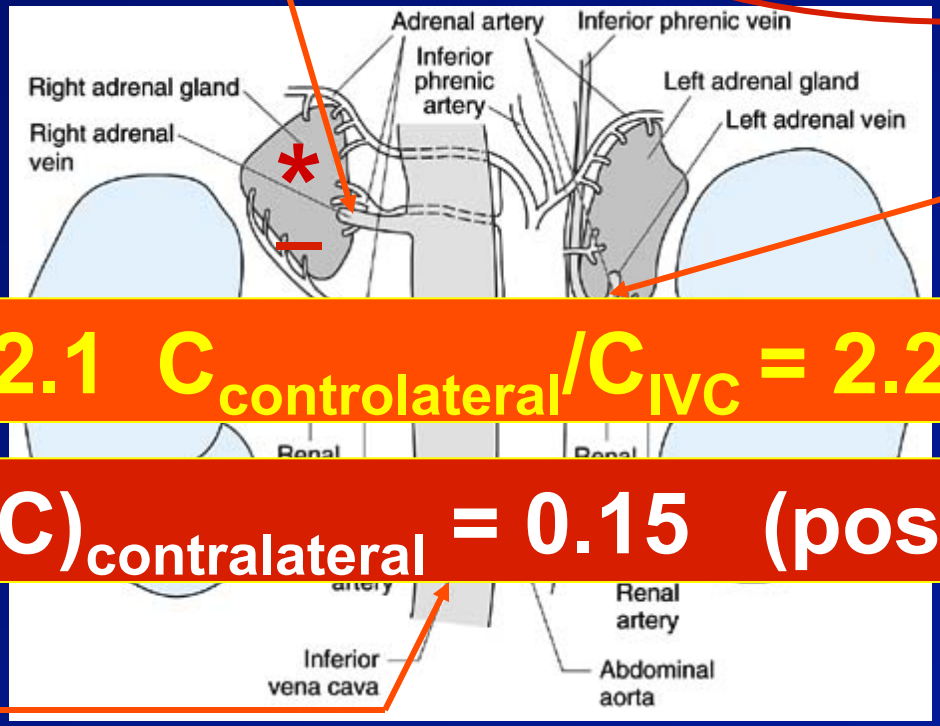
A/C = 16.3

Right adrenal vein

Aldosterone = 1433 pg/ml
Cortisol = 13.1 µg/dl

A/C = 109.3

Left adrenal vein



$C_{side}/C_{IVC} = 2.1$ $C_{controlateral}/C_{IVC} = 2.2$ (v.n.>2)

$(A/C)_{side}/(A/C)_{contralateral} = 0.15$ (positive if > 4)

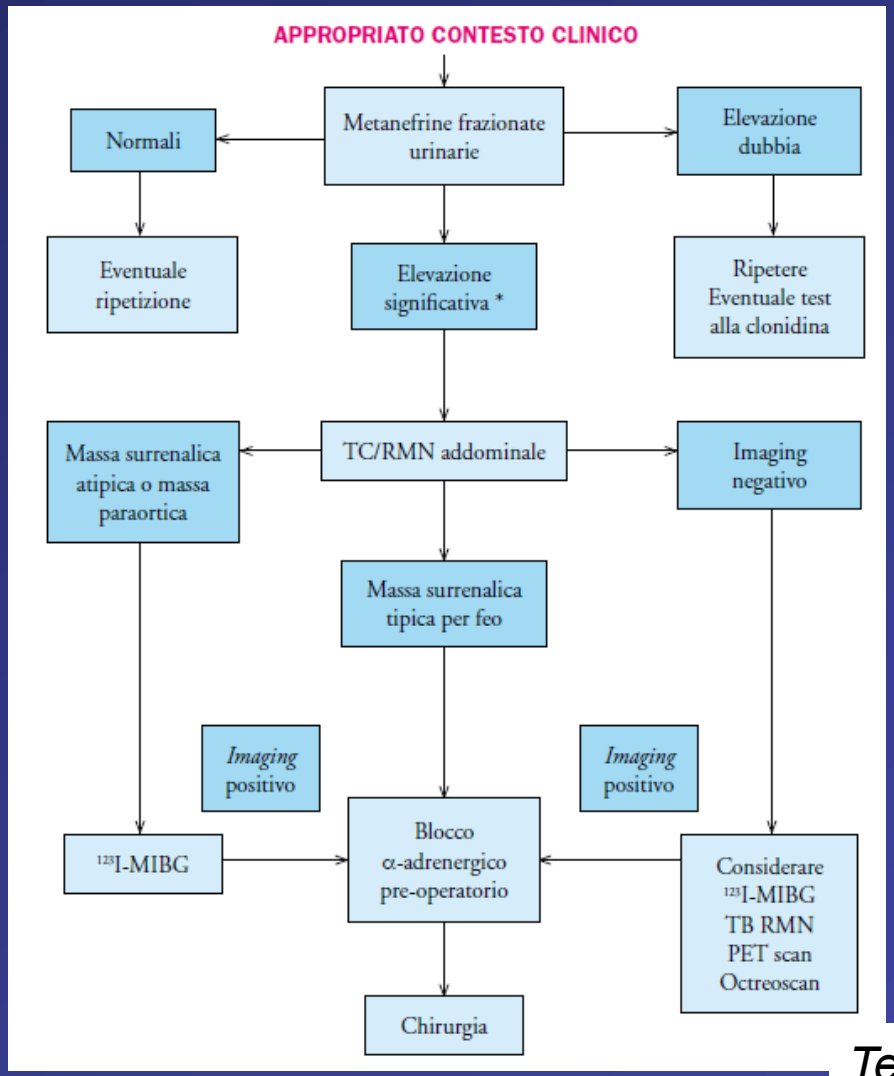
Inferior vena cava

Aldosterone = 195 pg/ml
Cortisol = 6.0 µg/dl

A quali pazienti proporlo?

1. Identificare i pazienti che possono essere sottoposti ad intervento rispetto a quelli che possono beneficiare della terapia medica.
2. Nei pazienti con TC surreni negativa, la valutazione della risposta alla terapia medica può permettere di identificare meglio coloro da inviare ad AVS, laddove la terapia chirurgica sia indicata e desiderata.
3. Per i pazienti con TC surreni positiva considerare due elementi: età e il rischio di un incidentaloma surrenalico, dal momento che quest'ultimo è estremamente ridotto nei soggetti con età <40 anni.
4. Criteri per adenoma (nodo alla CT, ipoK, marcata elevazione ARR, HTN grado 3) ???

FEOCROMOCITOMA

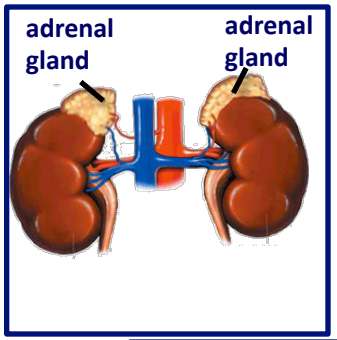


Terzolo, Reimondo, 2008

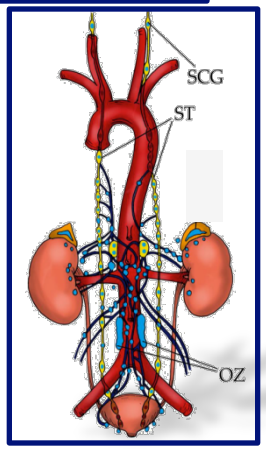
NOSOLOGY

Pheochromocytoma: → **sympathetic in origin**

s-PGL → **intra-adrenal**



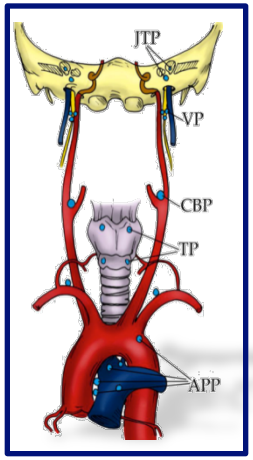
Paraganglioma → **extra-adrenal:** **abdominal**
thoracic



parasympathetic in origin

HN-PGL

Head / Neck: **Carotid body tumor**
vagal PGL
jugular PGL
tympanic PGL



Chi sottoporre a valutazione biochimica

- Pazienti con segni e sintomi suggestivi per feo
- Pazienti con (recente insorgenza di) ipertensione di difficile controllo o resistente alla terapia
- Paziente con inspiegata variabilità della PA
- Pazienti con ipotensione ortostatica spontanea
- Ipertensione parossistica dopo interventi chirurgici e anestesia o farmaci (BB, steroidi)
- Pazienti con predisposizione genetica per feo
- Pazienti con incidentaloma surrenalico (± ipertensione)

Phaeochromocytoma
Lancet 2005; 366: 665–675
Jacques W M Lenders, Graeme Eisenhofer, Massimo Mannelli, Karel Pacak

Chi sottoporre a valutazione biochimica

- Pazienti con segni e sintomi suggestivi per feocromocitoma
- Pazienti con recente insorgenza di ipertensione di difficile controllo o resistente alla terapia
- Pazienti con comparsa di ipertensione parossistica durante interventi chirurgici e anestesia
- Pazienti con predisposizione genetica per feocromocitoma
- Pazienti con incidentaloma surrenalico
- Pazienti con improvvisi attacchi d'ansia

- **In considerazione della bassa prevalenza del feocromocitoma, non vi è indicazione allo screening biochimico in pazienti asintomatici con ipertensione.**

Phaeochromocytoma
Lancet 2005; 366: 665–675
Jacques W M Lenders, Graeme Eisenhofer, Massimo Mannelli, Karel Pacak

CLINICA

Sintomi tipici delle **crisi parossistiche**, legate a un brusco rilascio delle catecolamine:

- Cefalea
- Cardiopalmo
- Sudorazione
- Pallore
- Ipertensione parossistica

5 al 15% delle masse surrenaliche di riscontro occasionale → feocromocitomi

↓

> 50% non causano Ipertensione

Altri sintomi

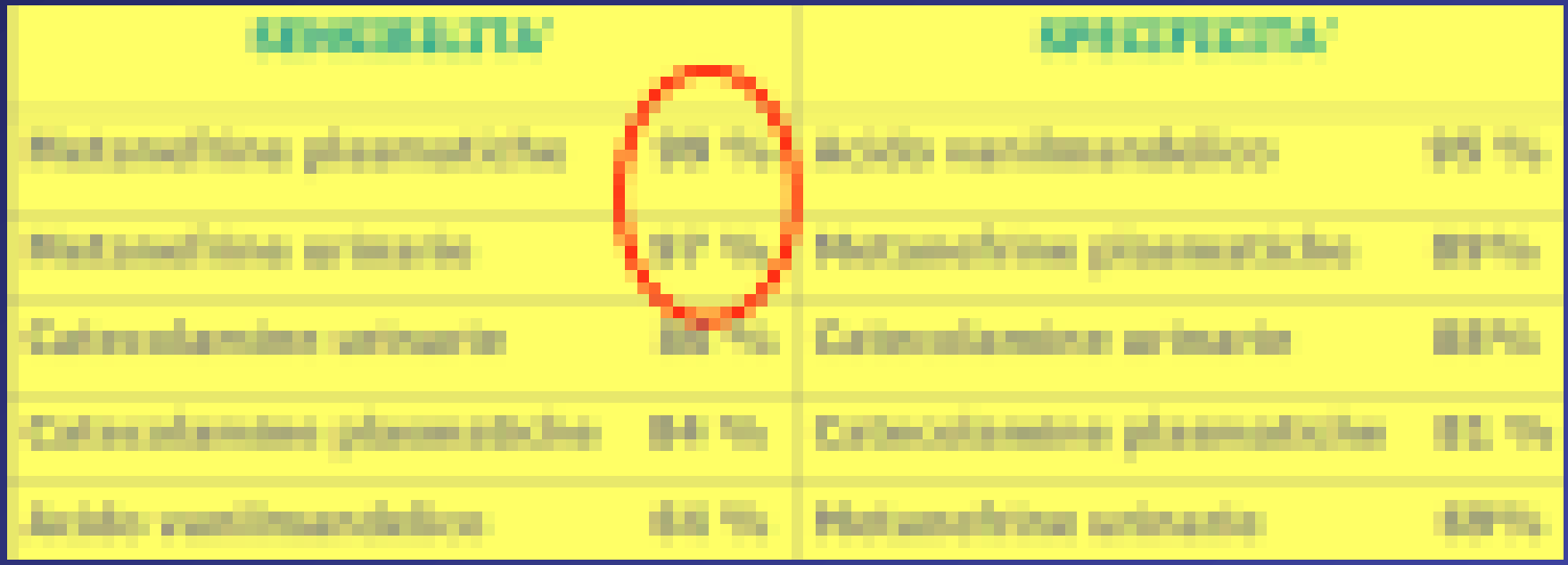
- Ipertensione p
- Ipotensione or
- Naus
- *Flush*
- Calo
- Aster
- Ansia
- Iperglicemia
- Incidentaloma surrenali
- Sintomi neurologici compressivi (tipici dei paragangliomi capo-collo non secrenenti)
- Sindromi familiari (MEN II, VHL, NF1, SPG)

TRIADE CLASSICA

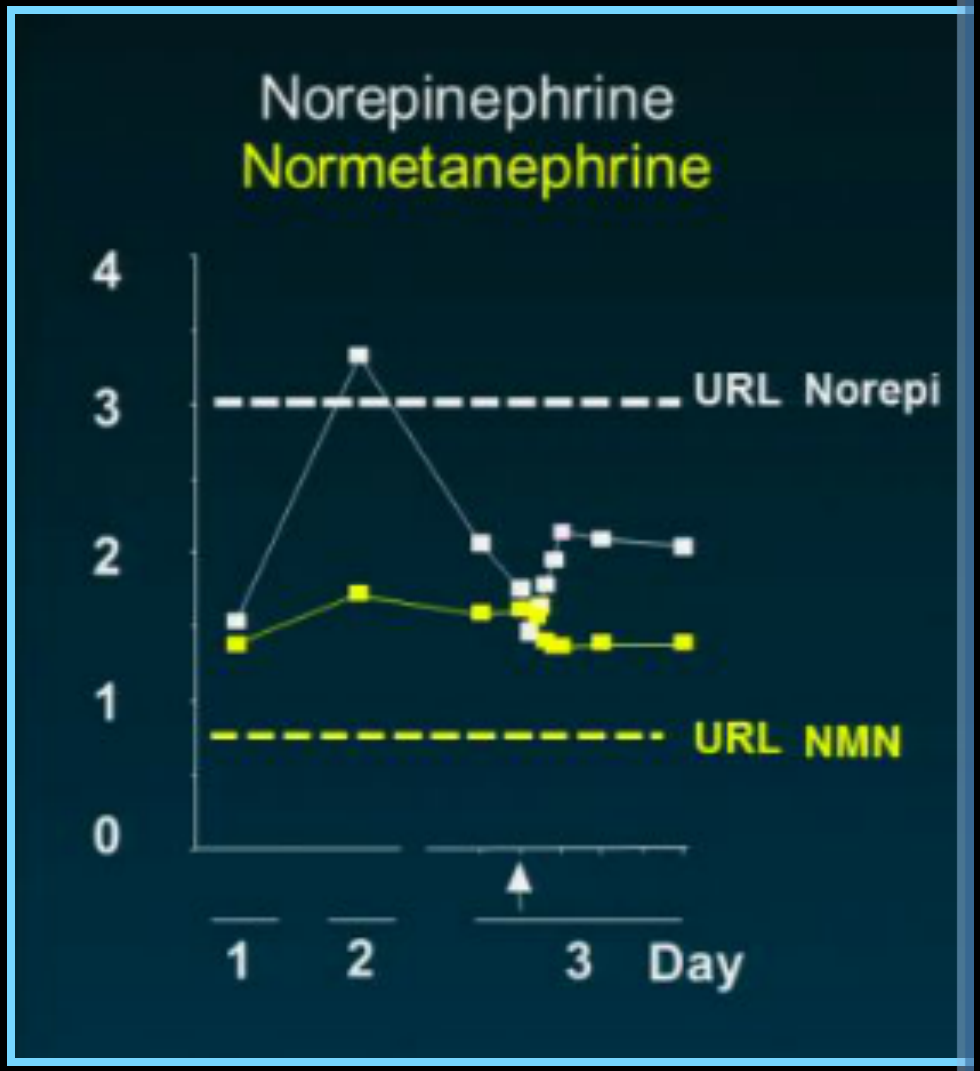
	Frequency
Headache	60–90%
Palpitations	50–70%
Sweating	55–75%

6% Feo

BIOCHIMICA



Lenders JW. et al JAMA 2002: 287(11):1427-34



Metanephrines are secreted constantly and not episodically as catecholamines

Causes of false-negative and false-positive test results

false-negative test results

- *very small tumors may be 'silent'*
- *24-hrs urine collections may be incomplete*

false-positive test results

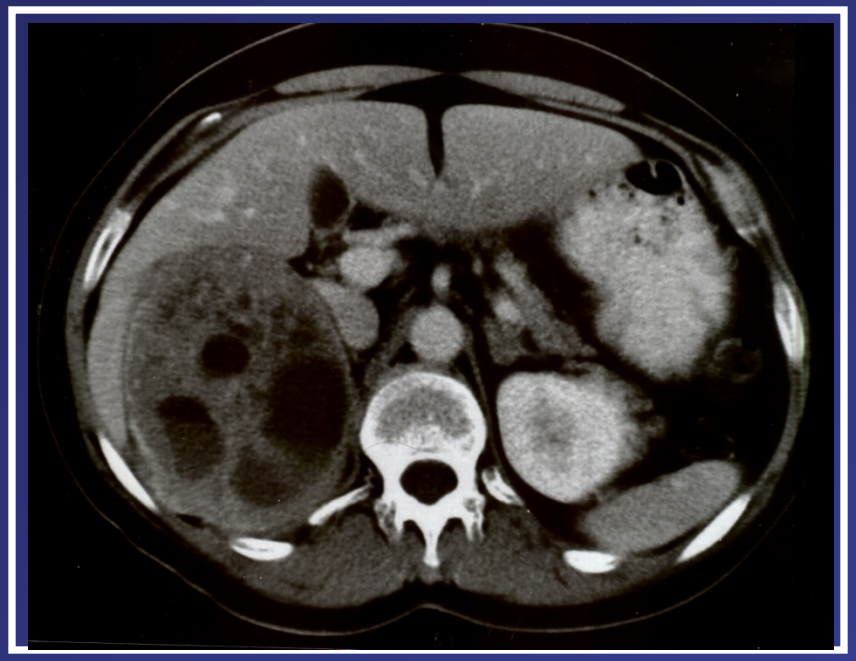
- *elevations in catecholamines or metabolites are not specific for pheochromocytoma*

Interferenze con il dosaggio

Pharmacodynamic or pharmacokinetic interference	
Tricyclic antidepressants	Blocks norepinephrine reuptake, causing rises in plasma and urinary norepinephrine, normetanephrine, and VMA
Phenoxybenzamine	Blocks presynaptic α2 adrenoceptors, causing increases in plasma and urinary norepinephrine, normetanephrine, and VMA
Monoamine oxidase inhibitors	Blocks deamination, causing up to five-fold increases in plasma and urinary metanephrines
Levodopa	Metabolised by enzymes that also convert catecholamines
α-methyldopa	Metabolised by enzymes that also convert catecholamines
Stimulants (eg, caffeine, nicotine)	Increased plasma and urinary catecholamines
Sympathomimetics (eg, amfetamines, ephedrine)	Increased plasma and urinary catecholamines
Calcium-channel blockers (dihydropyridines)	Increased plasma catecholamines due to sympathetic activation

Labetalol, sotalol, acetaminophen may cause false posiive results

Silent Pheochromocytoma



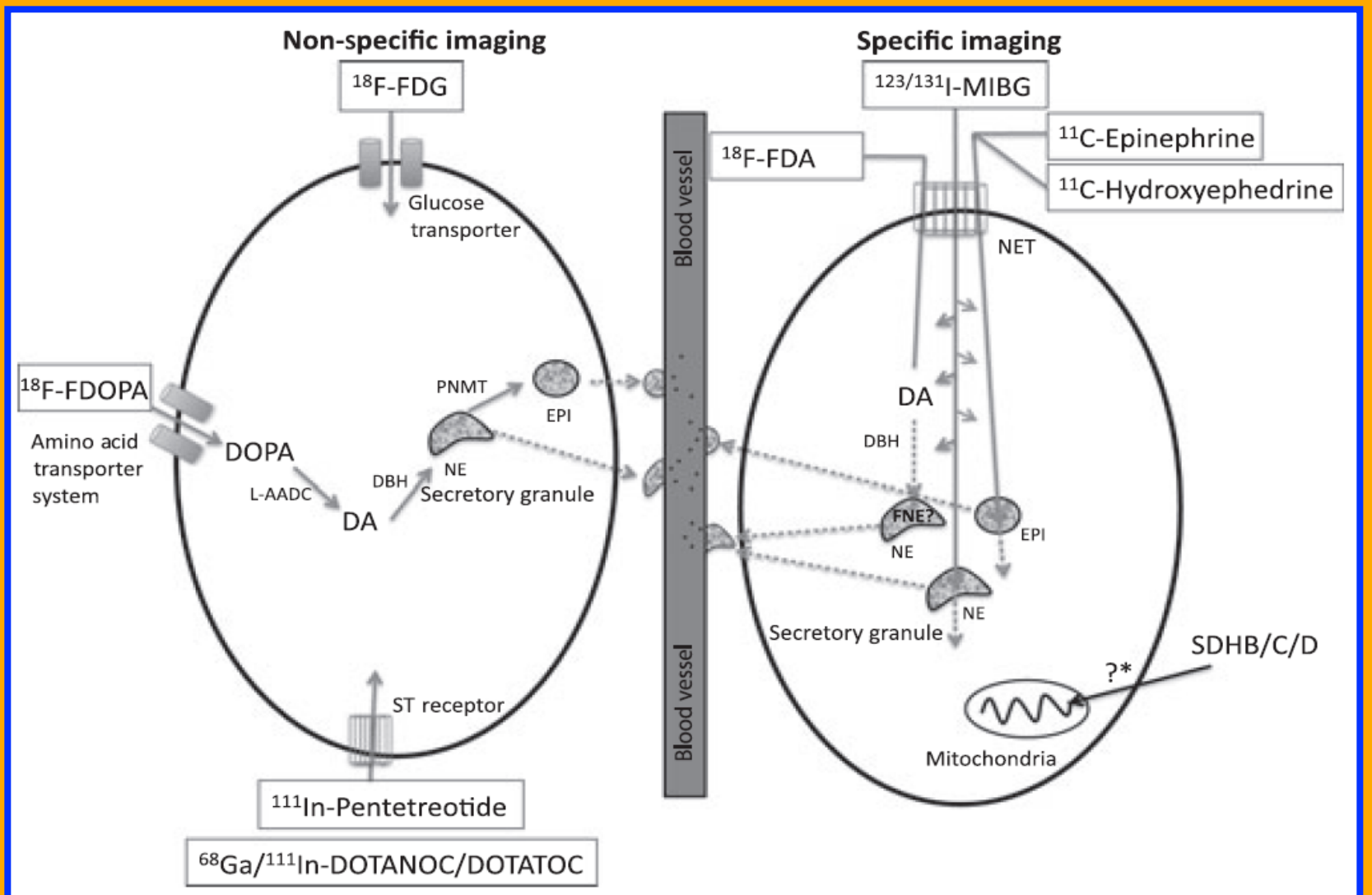
About 50% of patients with incidentally detected pheo are normotensive or have low-grade hypertension.

Mantero et al., 2000
Bulow & Ahren, 2002

Up to 80% of patients with unsuspected pheo who underwent surgery or anesthesia have died.

Kloos et al., 1995

IMAGING



Havekes B. *New imaging approaches to phaeochromocytomas and paragangliomas*. Clin Endocrinol 2010; 72, 137-145

Endocr Pract. 2010 May-Jun;16(3):398-407.

Clinical use and utility of metaiodobenzylguanidine scintigraphy in pheochromocytoma diagnosis.

Lev I, Kelekar G, Waxman A, Yu R

- Sensitivity was 73% and specificity was 69% if any adrenal uptake was considered positive
- False results were more common in younger patients, but not correlated with biochemical test results
- In patients with pheochromocytoma either excluded or confirmed, the MIBG scintigraphy results were confirmatory in 63%, but misleading in 37%.
- MIBG scintigraphy results did not provide additional diagnostic value to any case and contributed to pheochromocytoma overdiagnosis and even unnecessary adrenalectomy.

Comparison of ^{18}F-Fluoro-L-DOPA, ^{18}F-Fluoro-Deoxyglucose, and ^{18}F-Fluorodopamine PET and ^{123}I-MIBG Scintigraphy in the Localization of Pheochromocytoma and Paraganglioma

Henri J. L. M. Timmers, Clara C. Chen, Jorge A. Carrasquillo, Millie Whatley, Alexander Ling, Bastiaan Havekes, Graeme Eisenhofer, Lucia Martiniova, Karen T. Adams, and Karel Pacak*

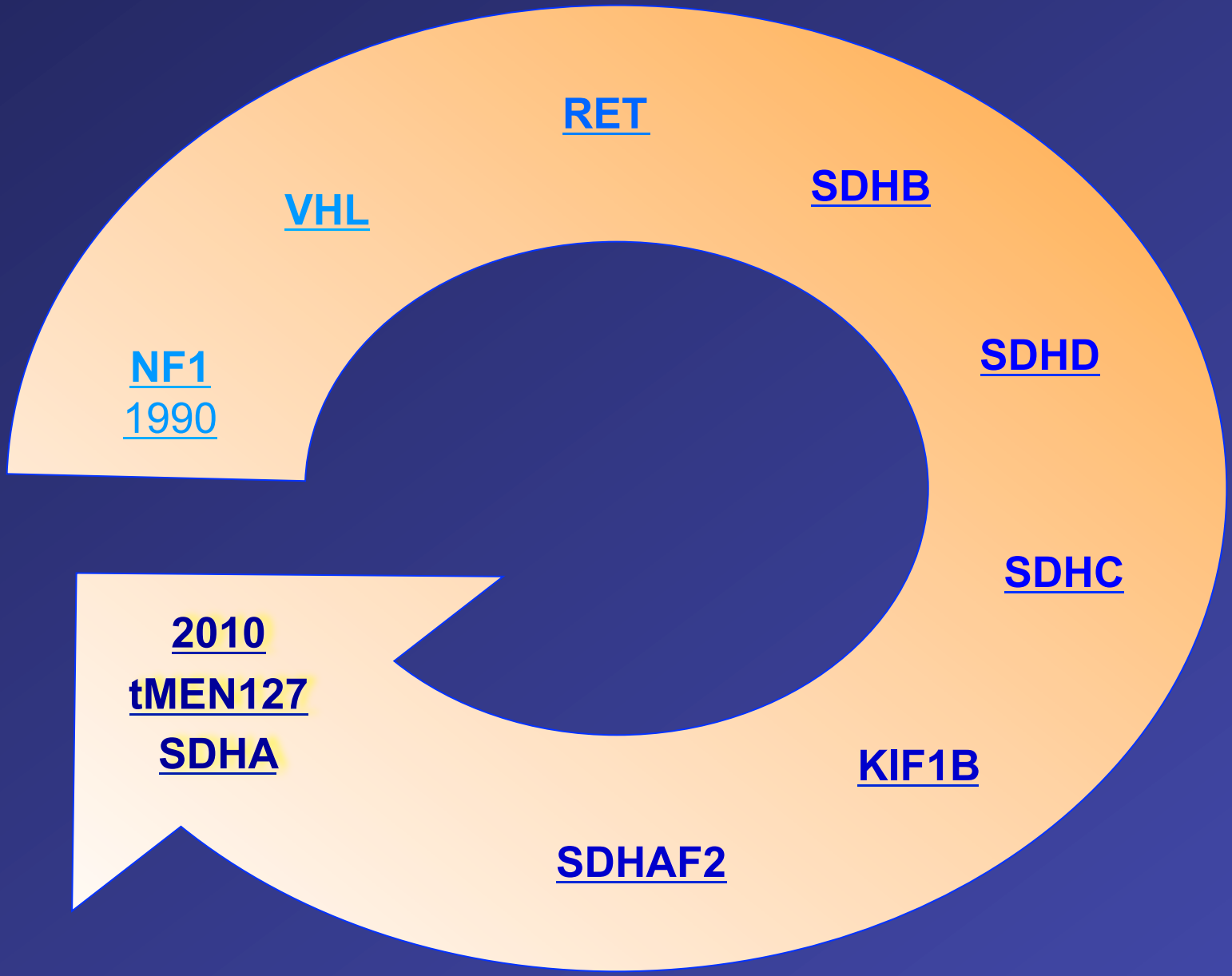
TABLE 4. Sensitivity

	CT and/or MRI	^{18}F-DOPA	^{18}F-FDA	^{123}I-MIBG	^{18}F-FDG
Nonmetastatic PGL (20 patients)					
In reference to histologically confirmed lesions	100% (26/26)	81% (21/26)	77% (20/26)	77% (20/26)	88% (23/26)
Sensitivities are not significantly different between functional imaging modalities					
	CT and/or MRI	**^{18}F-DOPA^{A}**	**^{18}F-FDA^{B}**	**^{123}I-MIBG^{C}**	**^{18}F-FDG^{D}**
Metastatic PGL (28 patients)					
In reference to lesions on CT and/or MRI		45% (96/211)	76% (161/211)	57% (106/187)	74% (157/211)

A *vs.* B, A *vs.* C, A *vs.* D, B *vs.* C, C *vs.* D: $P < 0.01$; B *vs.* D: $P = 0.760$.

18F-FDA PET/CT is the preferred technique for the localization of the primary PGL and to rule out metastases.
Second best, equal alternatives are 18F-DOPA PET and 123I-MIBG scintigraphy.

GENETICA


RET
SDHB
VHL
NF1
1990
SDHD
SDHC
2010
tMEN127
SDHA
KIF1B
SDHAF2

GENETICA

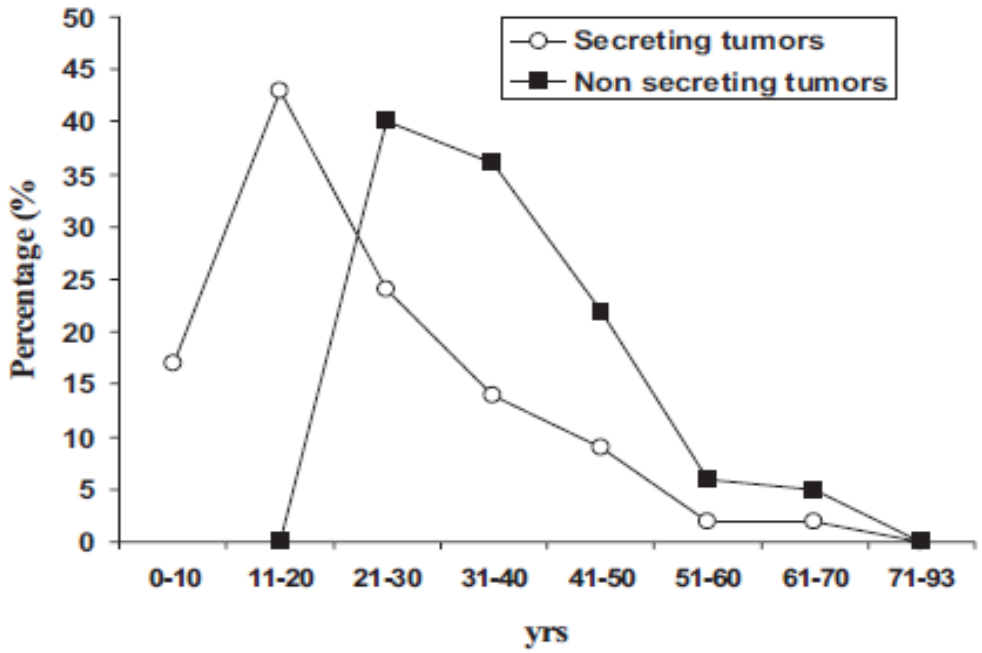


FIG. 1. Percentage incidence of mutations per decades of ages in patients with clinically sporadic secreting tumors (Pheos and sPGLs) (*open circles*) and patients with clinically sporadic nonsecreting tumors (HNPGLs) (*closed squares*).

Mannelli *et al.* Genetic Screening of Pheochromocytoma
J Clin Endocrinol Metab, May 2009, 94(5):1541–1547

Quando è indicato lo screening genetico?

- Co-presenza di multipli tumori diversi nello stesso paziente
- Feo/PGL multifocale/bilaterale
- Età < 40 anni
- Presentazione “sindromica” nel paziente o nella famiglia

CONCLUSIONI

- Le indagini biochimiche devono sempre precedere le indagini radiologiche
- Bisogna disporre di un laboratorio affidabile
- Selezionare i pazienti ad elevata probabilità pre-test di malattia

GRAZIE per l'ATTENZIONE

DOMANDE…