WORK-UP DIAGNOSTICO DELLA SINDROME DI CUSHING: STATO DELL'ARTE

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WORKUP DIAGNOSTICO DELLA SINDROME DI CUSHING

- Il sospetto clinico
- Identificazione delle popolazioni a rischio
- Screening tests
- Sindrome di Cushing vs pseudo Cushing
- Diagnosi eziologica
- Valutazione remissione
- Valutazione della recidiva

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

J Clin Endocrinol Metab, May 2008, 93(5):1526–1540

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

Symptoms	Signs	Overlapping conditions
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")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
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	

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

- Patients with unusual features for age (*e.g.* osteoporosis, hypertension) (Table 1) (1⊕⊕◯◯)
- Patients with multiple and progressive features, particularly those who are more predictive of Cushing's syndrome (Table 1) (1⊕⊕◯◯)
- Children with decreasing height percentile and increasing weight (1⊕◯◯◯)
- Patients with adrenal incidentaloma compatible with adenoma (1⊕◯◯◯).

3.3 We recommend against widespread testing for Cushing's syndrome in any other patient group (1⊕◯◯◯).

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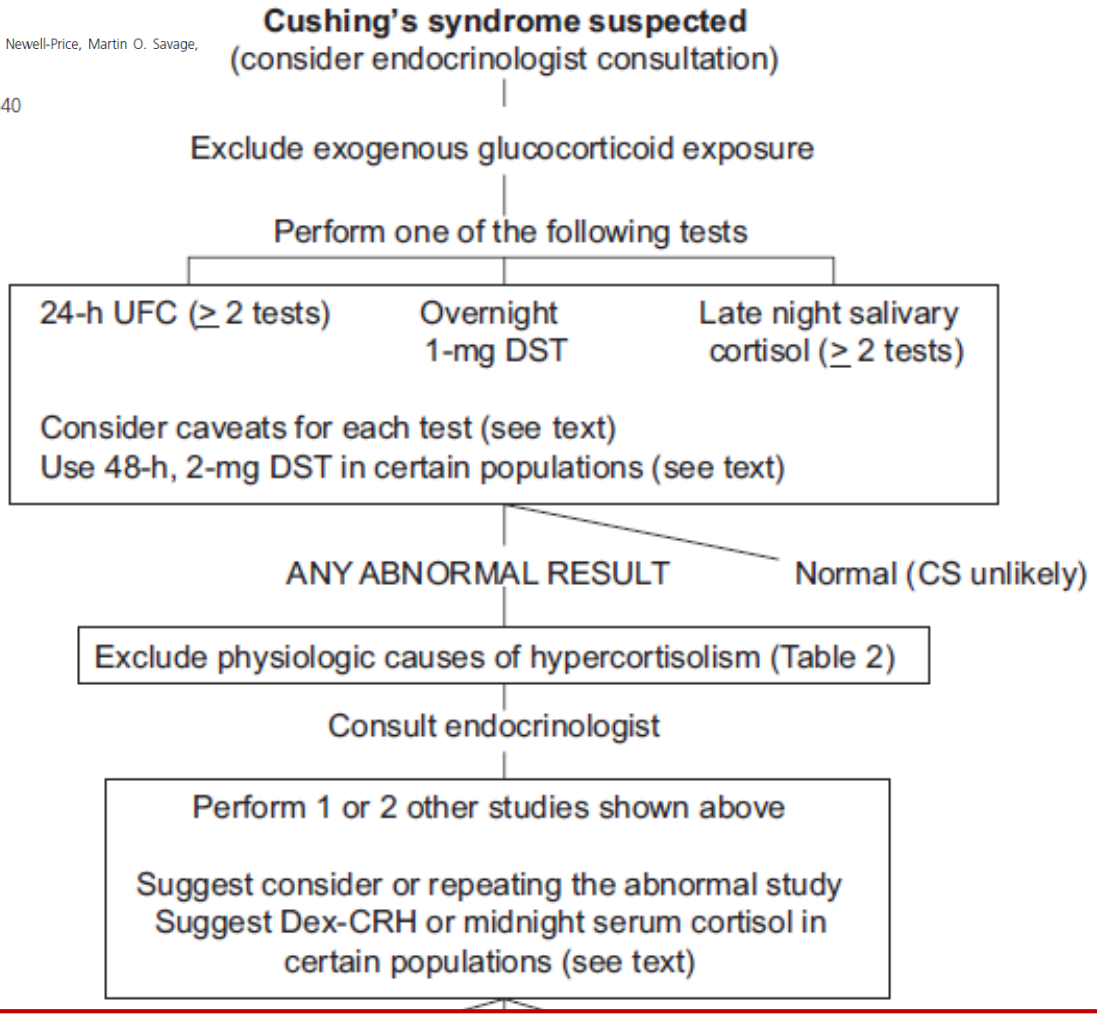


3.9.2 We suggest against the use of the desmopressin test, except in research studies, until additional data validate its utility (2⊕○○○).

European Journal of Endocrinology (2010) **163** 9–13

INVITED COMMENTARY

The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective

Laurence Guignat[1] and Jérôme Bertherat[1,2,3]

The Endocrine Society guideline restricts the desmopressin test to research studies only. However, in several publications mainly from Italy, the desmopressin test had a better diagnosis accuracy (10, 17, 18), than that of Dex–CRH test, even in patients with mild hypercortisolism. In addition, desmopressin is cheaper than CRH, and the test procedure is less cumbersome than that of the Dex–CRH test.

JOHN NEWELL-PRICE
ASHLEY B. GROSSMAN

Differential Diagnosis of Cushing's Syndrome

Arq Bras Endocrinol Metab 2007;51/8

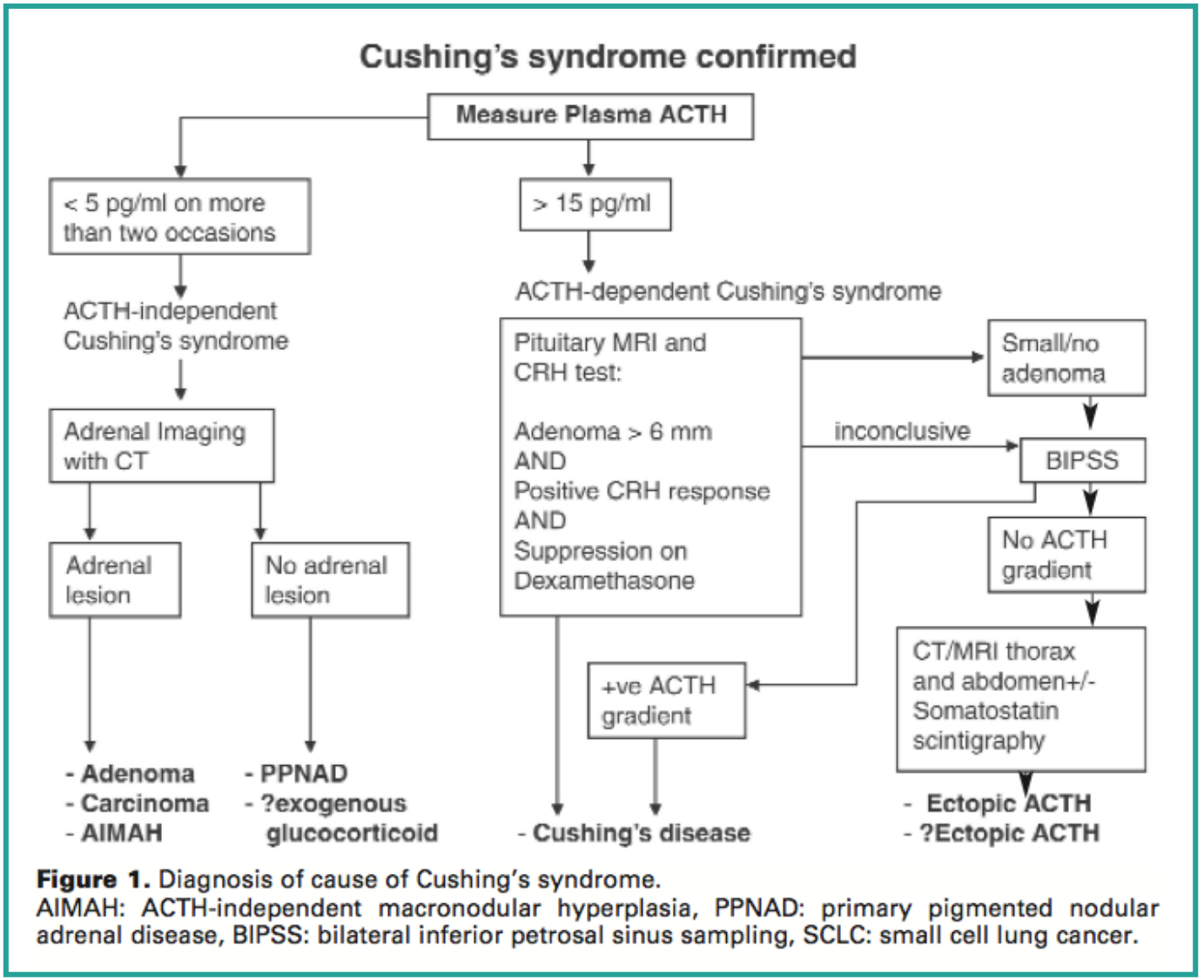


Figure 1. Diagnosis of cause of Cushing's syndrome.
AIMAH: ACTH-independent macronodular hyperplasia, PPNAD: primary pigmented nodular adrenal disease, BIPSS: bilateral inferior petrosal sinus sampling, SCLC: small cell lung cancer.

…al 2017…

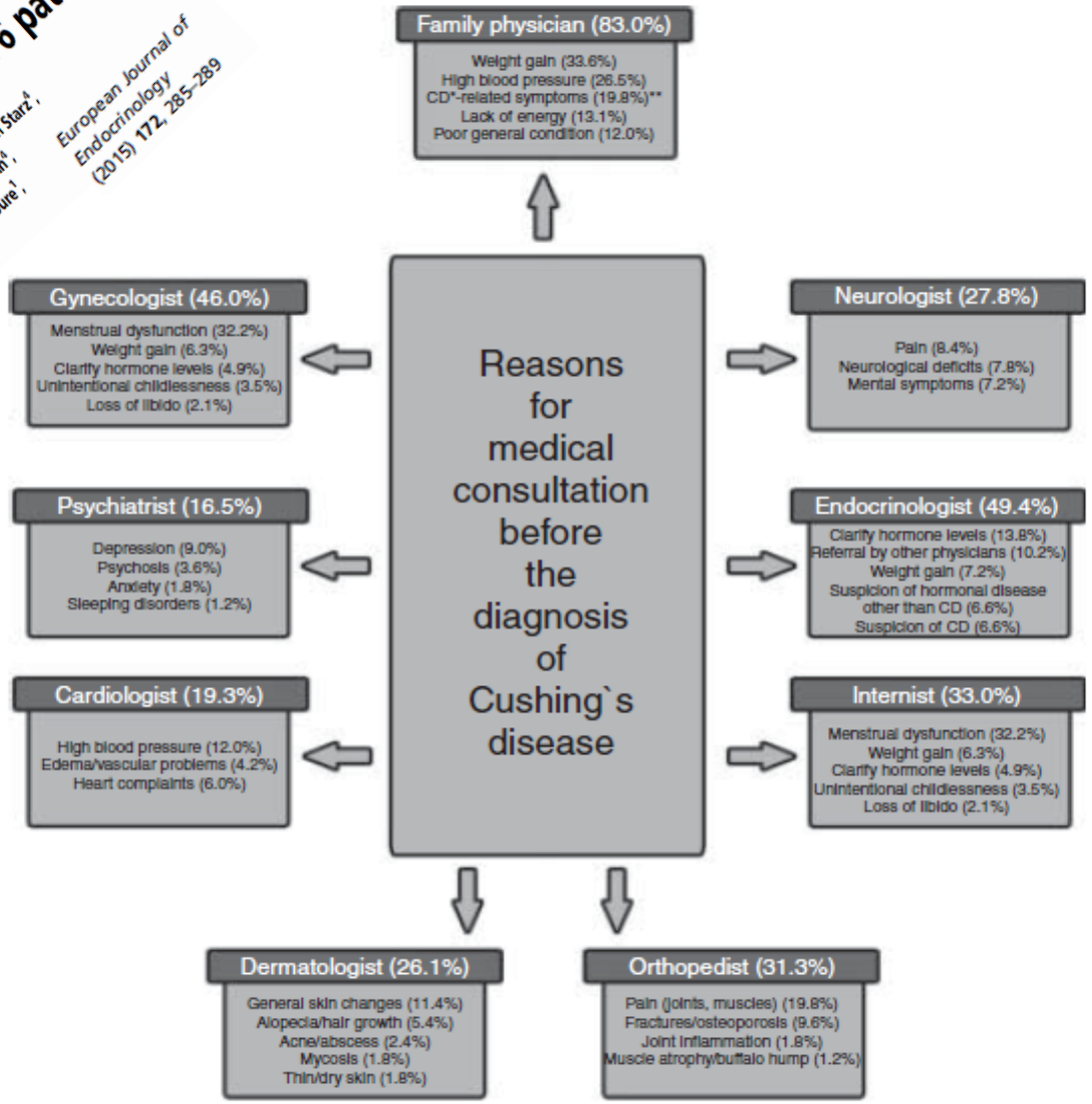
nessun aggiornamento LG-ES
nessuna nuova LG

Sospetto clinico e popolazioni a rischio

From first symptoms to final diagnosis of Cushing's disease: experiences of 176 patients

Ilonka Kreitschmann-Andermahr[1], Tsambika Psaras[2], Maria Bisogka[3], Daniel Starz[4], Bernadette Kleist[1], Sonja Siegel[1,4], Monika Milian[5], Johannes Kohlmann[4], Christa Menzel[4], Dagmar Führer-Sakel[3], Jürgen Honegger[5], Ulrich Sure[1], Oliver Müller[1] and Michael Buchfelder[4]

European Journal of Endocrinology (2015) 172, 285–289



From first symptoms to final diagnosis of Cushing's disease: experiences of 176 patients

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European Journal of Endocrinology
(2015) **172**, 285–289

Table 1 Different medical specialties named by the study participants as the ones who made the definite diagnosis of CD.

Physician	Number of subjects (*n*)	Percentage of subjects (%)
Endocrinologist	123	69.9
Internist	18	10.2
Family physician	11	6.3
Neurologist	5	2.8
Gynecologist	4	2.3
Orthopedist	1	0.6

suggest to specifically train FPs and general practitioners to look for rare or not age-appropriate symptom combinations like buffalo hump, plethora, striae, proximal muscle weakness, and signs of osteoporosis in patients with weight gain. Early referral of such patients to an endocrinologist is then mandatory to facilitate timelier diagnosis.

Cushing's syndrome: update on signs, symptoms and biochemical screening

Lynnette K Nieman

European Journal of Endocrinology
(2015) 173, M33–M38

A Cushing's syndrome index

Nugent *et al.* (35) advanced this idea in 1964, stating 'In the differential diagnosis … [of Cushing's syndrome], the physician uses clinical signs and simple laboratory data in addition to information … from past experiences to make a decision concerning the probability of the diagnosis'. The

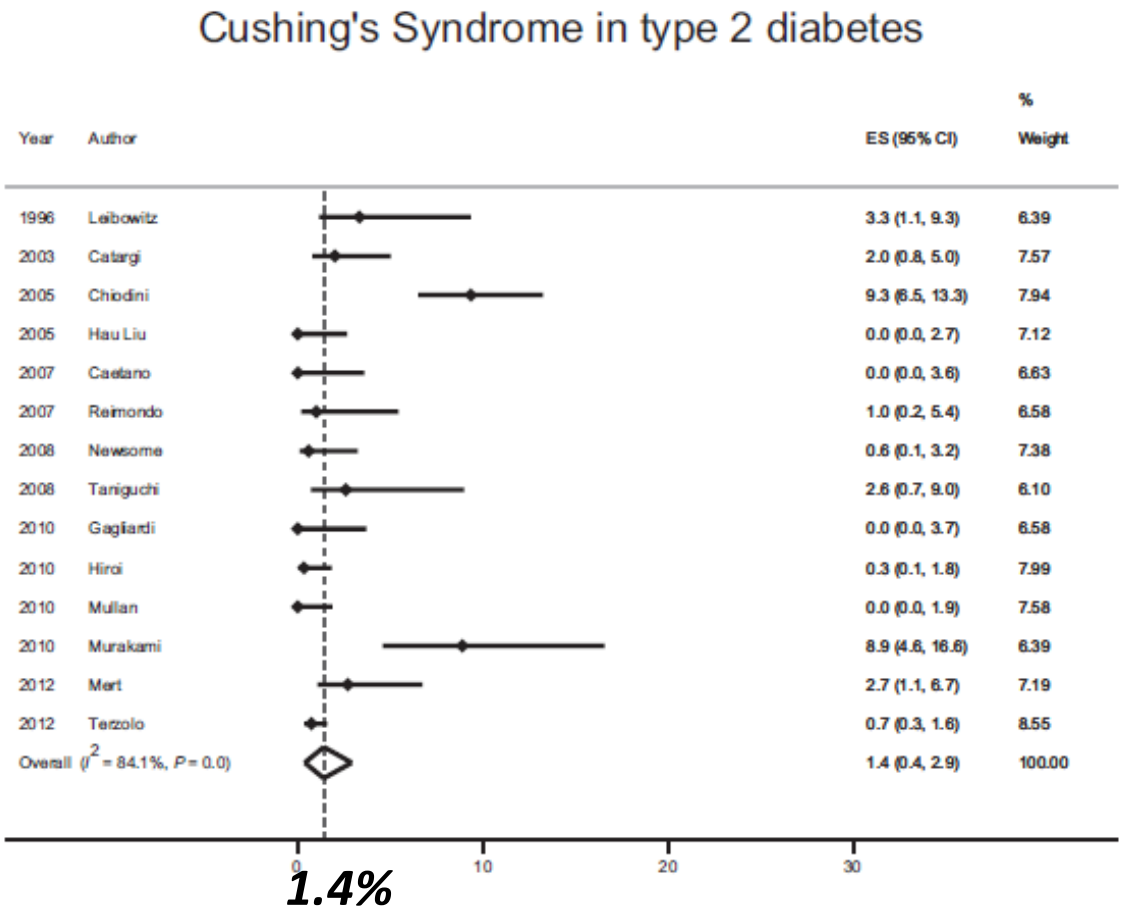
Unfortunately, the results of this Bayesian analysis do not give high positive (16%) and negative (61%) predictive values. However, the concept of an 'index' deserves to be reevaluated with current data.

DIAGNOSIS OF ENDOCRINE DISEASE

Prevalence of hypercortisolism in type 2 diabetes patients: a systematic review and meta-analysis

Charlotte Steffensen[1], Alberto M Pereira[2], Olaf M Dekkers[2,3,4] and Jens Otto L Jørgensen[1]

European Journal of Endocrinology
(2016) **175**, R247–R253



Endogenous subclinical hypercortisolism and bone: a clinical review

I Chiodini[1], **C Eller Vainicher**[1], **V Morelli**[1,2], **S Palmieri**[1,2], **E Cairoli**[1,2], **A S Salcuni**[3], **M Copetti**[4] and **A Scillitani**[5]

European Journal of Endocrinology
(2016) **175**, R265–R82

Table 2 Summary of the available studies investigating the prevalence of subclinical hypercortisolism (SH) in patients with apparently primary osteoporosis.

Study	*n* (F/M)	Population	Screening test	Cutoff	Prevalence (%)			
					Overall	In patients with low BMD	In patients with fragility fracture	In patients with low BMD and/or fragility fracture
Kann *et al.* (2001) (116)[a]	78 (78/0)	Osteoporosis and fragility fracture	3 mg DST	2.0 µg/dL	3.8 (3/78)	NA	3.8 (3/78)	NA
Tannebaum *et al.* (2002) (117)[b]	173 (173/0)	Osteoporosis	UFC	NA	0.6 (1/173)	0.6 (1/173)	NA	NA
Chiodini *et al.* (2007) (30)[c]	219 (200/19)	Normal BMD (n=72), osteopenia or osteoporosis (n=147)	1 mg DST	1.8 µg/dL	3.2 (7/219)	9.9 (7/71)	10.8 (7/65)	4.8 (7/147)
Eller-Vainicher *et al.* (2013) (118)[d]	602 (563/39)	Osteoporosis and/or fragility fracture	1 mg DST	1.8 µg/dL	1.3 (8/602)	1.7 (7/412)	1.9 (7/361)	NA
Lasco *et al.* (2014)[d] (119)	50 (50/0)	NA	1 mg DST	1.8 µg/dL	1.5 (3/50)	NA	17.6 (3/8)	NA

Screening for Cushing's syndrome: Is it worthwhile?

Ilan Shimon

Pituitary (2015) 18:201–205

Routine screening for CS is not worthwhile or cost-effective for patients with morbid obesity, type 2 DM or hypertension, where it usually detects less than 1 % of

ALGORITMO PER IL SOSPETTO CLINICO DI CS ??

Patients with vertebral osteoporosis and fractures may benefit from screening for cortisol excess, and patients with adrenal masses/adenomas should have endocrine work-up to exclude adrenal hypersecretion.

…no discostamento dalle LG 2008…

A Probabilistic Model for Cushing's Syndrome Screening in At-Risk Populations: A Prospective Multicenter Study

Antonio León-Justel, Ainara Madrazo-Atutxa, Ana I. Alvarez-Rios, Rocio Infantes-Fontán, Juan A. Garcia-Arnés, Juan A. Lillo-Muñoz, Anna Aulinas, Eulàlia Urgell-Rull, Mauro Boronat, Ana Sánchez-de-Abajo, Carmen Fajardo-Montañana, Mario Ortuño-Alonso, Isabel Salinas-Vert, Maria L. Granada, David A. Cano, and Alfonso Leal-Cerro, for the Spanish CRISALIDA Study Group*

J Clin Endocrinol Metab, October 2016, 101(10):3747–3754

Studio prospettico su 353 pz con almeno 2 segni/sintomi
(OB, ipertensione, DM non controllato, disturbi mestruali/androgenizzazione, osteoporosi)
219 non CS
26 CS (7.4%)

Table 4. Independent Diagnostic Indicators and Risk Score for CS

Variables	Regression Coefficient	*P* Value	Score Points
Osteoporosis	1.53	.004	2
Dorsocervical fat pad	1.81	.001	2
Muscular atrophy	3.4	<.001	3
LNSC			
Medium, 9.17–13.93 nmol/L	3.68	<.001	4
High, ≥13.93 nmol/L	4.93	<.001	5

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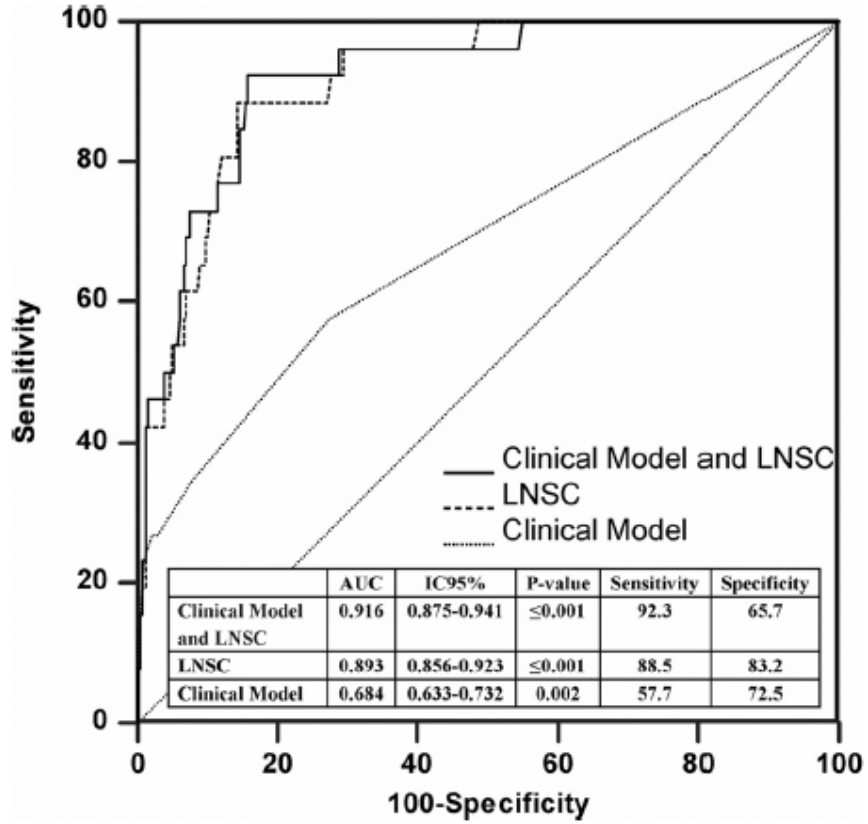


Figure 1. ROC curve of the clinical model, LNSC test, and the clinical model and LNSC in diagnosing CS.

Table 5. Total Number of Subjects and Prevalence of CS Per Score Category Using the Scoring System Obtained From the Combined Clinical and LNSC Model

	CS	
Score	No	Yes
0	199	0
2	69	1
3	3	0
4	36	8
5	9	2
6	9	2
7	2	6
8	0	0
9	0	3
10	0	1
11	0	1
12	0	2
Total	327	26

Total number… …atives, 1; true positives, 25; …

Sensibilità 96.2%
Specificità 82.9%

ITALIAN CUSHING-SCORE

- **Basato su parametri clinici**
-**Correlare positivamente** con la probabilità che il paziente sia affetto da sindrome di Cushing (tanto più alto/tanto più probabile)
-**Aumentare significativamente la probabilità pre-test** di avere la malattia
-**Indicare** in quali soggetti debba essere effettuato uno **screening ormonale** per identificare la malattia

- **Studio caso-controllo, multicentrico (ARCUS)**
- **Pazienti CS: 151** **(124 F e 27 M, età media 42,6±13,2)**
- **Controlli: 299** **(215 F e 84 M, età media 44,8±16,6)**
- **Prossimo invio per elaborazione statistica**

Diagnosi CS: screening e diagnosi differenziale

DEBATE:

IL CORTISOLO SALIVARE COME TEST DI SCREENING O COME MARKER DI MONITORAGGIO NELLA SINDROME DI CUSHING

- VANTAGGI E LIMITI

UN ASPETTO PECULIARE DELLA DIAGNOSI:

LA DIAGNOSI DIFFERENZIALE TRA CUSHING IPOFISARIO E CUSHING ECTOPICO

- RUOLO DEL LABORATORIO
- RUOLO DELL' IMAGING
- RUOLO DEL CATETERISMO DEI SENI PETROSI

Variability in laboratory parameters used for management of Cushing's syndrome

Endocrine (2015) 50:580–589

Francesca Pecori Giraldi[1,2] · Alberto G. Ambrogio[2]

Table 1 Issues associated with hormonal assays used in the management of Cushing's syndrome

Parameter	Sampling	Use	Specific issues	Possible solutions
Urinary free cortisol	Circadian secretion After 8 mg dexamethasone	Diagnosis Response to treatment Follow-up	Interference due to cortisol metabolites	Urine extraction, chromatographic assays
			Completeness of 24 h urine collection	Urinary creatinine
			Assay variability	Assay-specific cut-offs
	After CRH stimulation	Differential diagnosis	Increased CBG	Case history
Plasma ACTH	Morning	Differential diagnosis	Pulsatility, short half-life	Multiple sampling
			Assay-related variability	Assay standardization
	After CRH stimulation During IPSS	Differential diagnosis	No specific issue	

…measurements of cortisol in serum, urine or saliva and ACTH are subject to considerable variability, inherent to hormonal secretion and assay methodology…

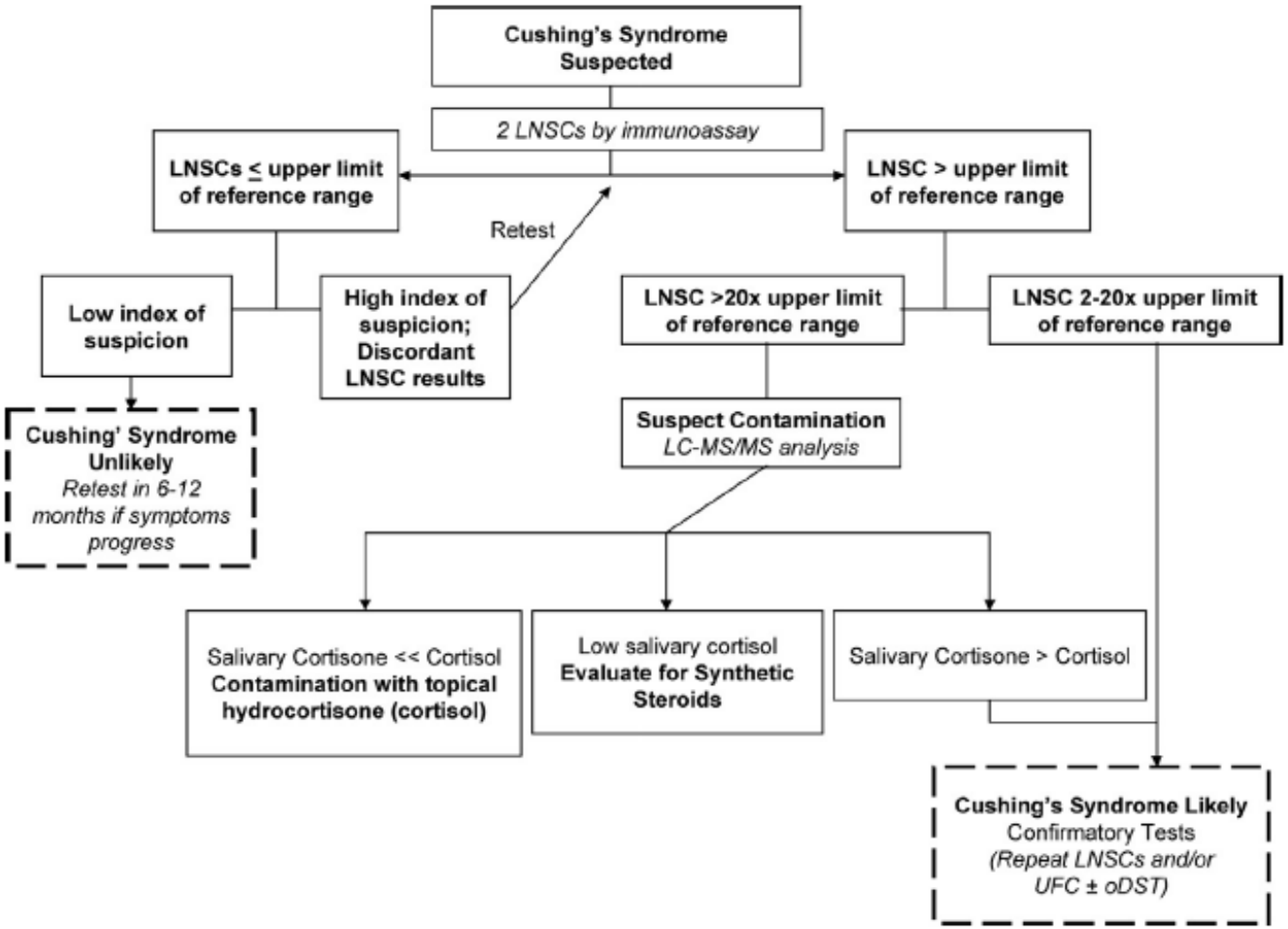
Altogether, interpretation of ACTH and cortisol measurements requires clinical expertise coupled with the knowledge that no single measurement is 100% accurate for the diagnosis and, by inference, management of Cushing's syndrome…

Cushing Syndrome

Update on Testing

Hershel Raff, PhD[a,b,c,d,*]

Endocrinol Metab Clin N Am 44 (2015) 43–50



REVIEW ARTICLE

Cushing's Syndrome: Screening and Diagnosis

Filippo Ceccato[1] · Marco Boscaro[1]

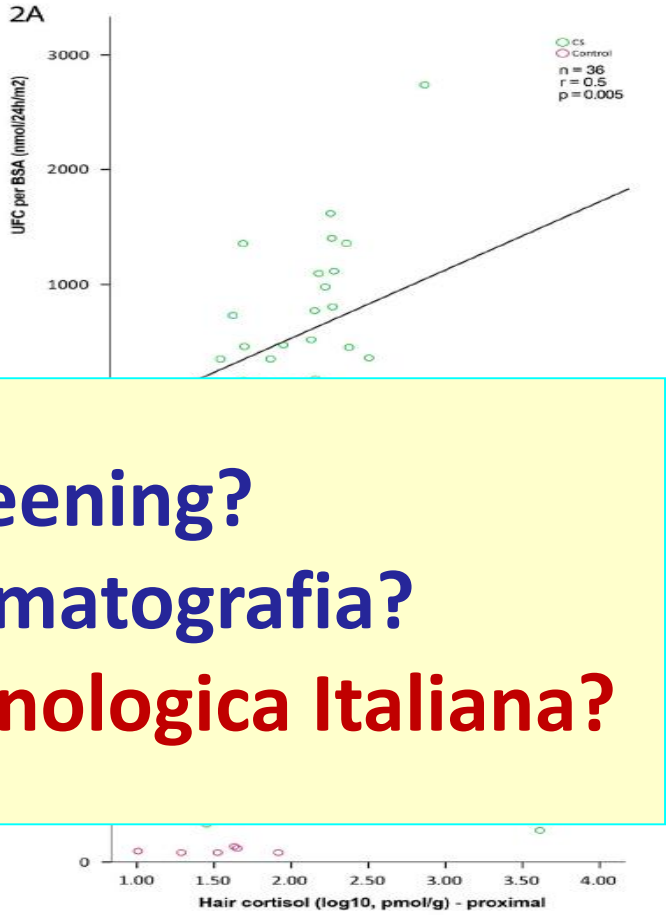
High Blood Press Cardiovasc Prev (2016) 23:209–215

Table 5 First-line tests by high-risk category (✔: suggested or recommended; ×: no evidence available, low-quality evidence or not recommended)

	DST	LNSC	UFC
Hypertension	✔	×	×
Diabetes mellitus	✔	×	×
Osteoporosis and/or bone fracture	✔	×	×
Pregnancy and estro-progestinic drugs	×	✔	✔
Anti-epileptic drugs	×	✔	✔
Renal failure (severe)	✔	✔	×
Cyclic CS	×	✔	✔
Subclinical CS (adrenal incidentaloma)	✔	×	×
Children and adolescents	✔	✔	✔

…qualche discostamento dalle LG 2008…

Hair cortisol in the evaluation of Cushing syndrome



Uno o più test di screening?

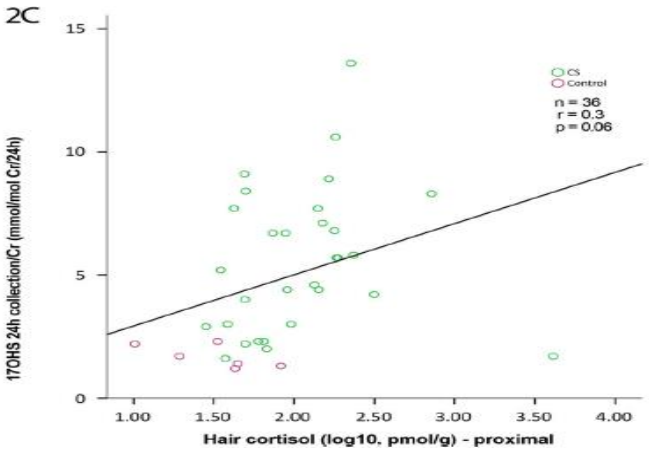
Immunoenzimatica o cromatografia?

Realtà nella Comunità Endocrinologica Italiana?

Cushing's syndrome

V.L. Wester, M. Reincke, J.W. Koper, E.L.T. van den Akker, L .Manenschijn, C.M. Berr, J. Fazel, Y.B. de Rijke, R.A. Feelders, E.F.C. van Rossum

Accepted 2017 as Manuscript EJE-16-0873



Cushing o Pseudo-Cushing?

TABLE 2. Conditions associated with hypercortisolism in the absence of Cushing's syndrome[a]

Conditions
Some clinical features of Cushing's syndrome may be present
Pregnancy
Depression and other psychiatric conditions
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus
Unlikely to have any clinical features of Cushing's syndrome
Physical stress (hospitalization, surgery, pain)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
CBG excess (increased serum but not urine cortisol)

[a] Whereas Cushing's syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.

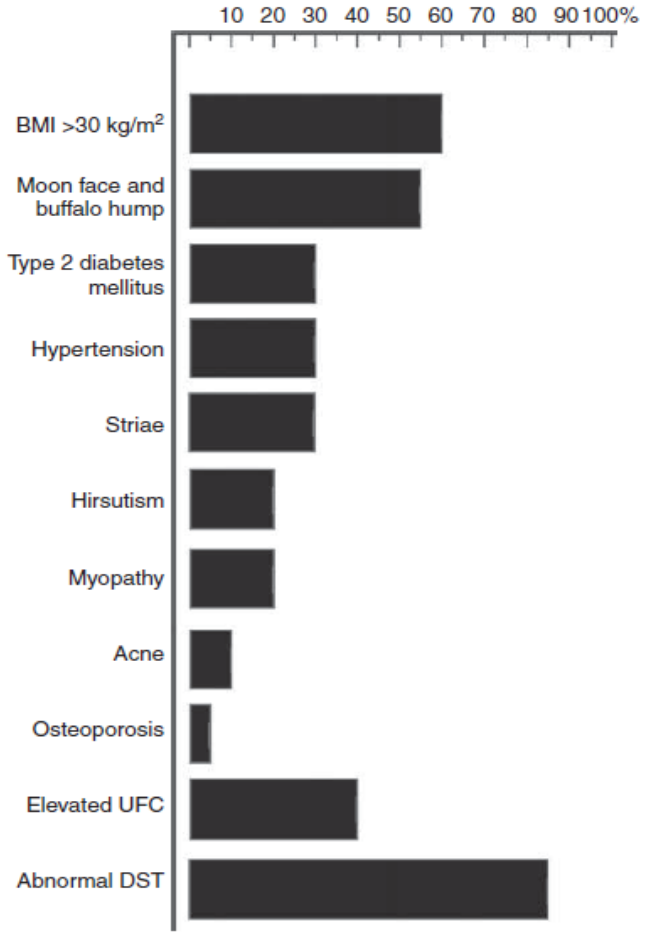


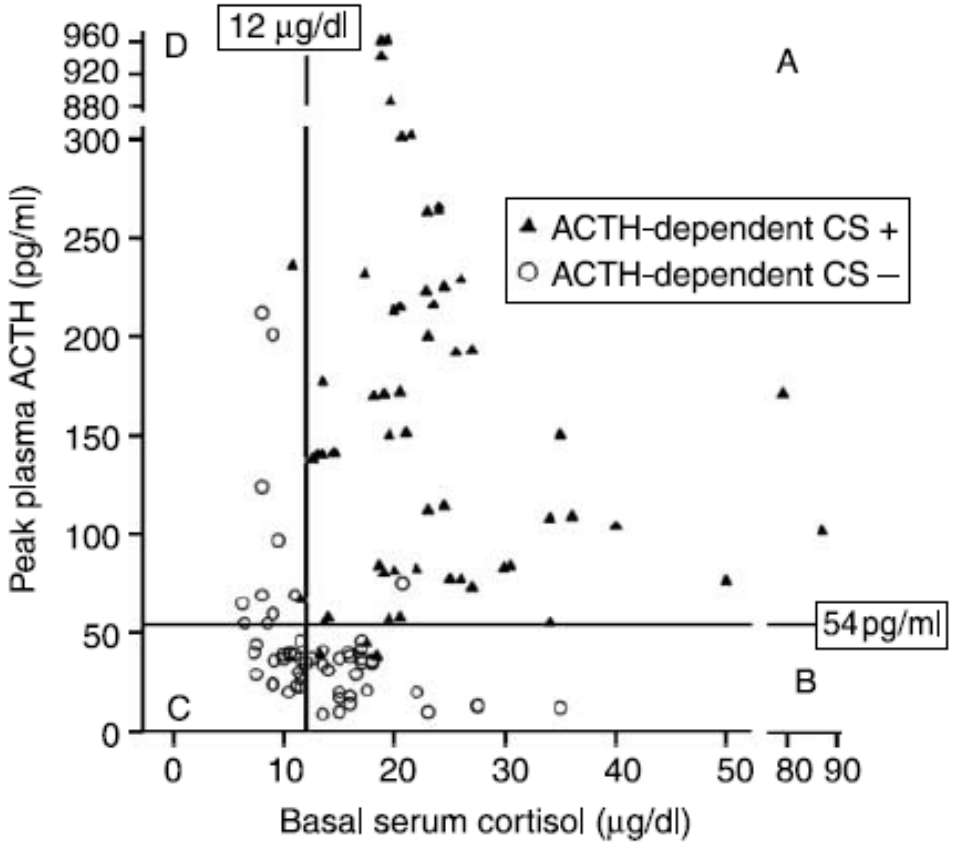
Figure 1
Block diagram showing the prevalence of various Cushingoid features in 20 patients with pseudo-Cushing's syndrome.

Use of the Desmopressin Test in the Differential Diagnosis of Pseudo-Cushing State from Cushing's Disease

J Clin Endocrinol Metab, March 2010, 95(3):1115–1122

Giacomo Tirabassi, Emanuela Faloia, Roberta Papa, Giorgio Furlani, Marco Boscaro, and Giorgio Arnaldi

Sensitivity 91.3%,
Specificity 98.2%



Use of the Desmopressin Test in the Differential Diagnosis of Pseudo-Cushing State from Cushing's Disease

J Clin Endocrinol Metab, March 2010, 95(3):1115–1122

Giacomo Tirabassi, Emanuela Faloia, Roberta Papa, Giorgio Furlani, Marco Boscaro, and Giorgio Arnaldi

TABLE 3. Diagnostic performance of the main tests in patients with mild hypercortisolism

	SE (CI) (%)	SP (CI) (%)	LR+	LR−	AUC_{LR} (CI_{AUC})
Mild-UFC-CD (n = 23) *vs.* PC (n = 28)					
OST serum cortisol: cutoff > 50 nmol/liter[b]	78.2 (56.3–92.5)	28.5 (13.2–48.6)[f]	1.09	0.76	0.68 (0.50–0.85)[h]
OST serum cortisol: cutoff > 138 nmol/liter[b]	65.2 (42.7–83.6)[g]	89.2 (71.7–97.7)	6.03	0.39	0.68 (0.50–0.85)[h]
Midnight serum cortisol > 207 nmol/liter[c]	86.9 (66.4–97.2)	64.2 (44–81.3)[f]	2.42	0.20	0.67 (0.51–0.83)[h]
DDAVP test[d]: basal serum cortisol > 331 nmol/liter[e] and Δ-ACTH > 4 pmol/liter[e]	86.9 (66.4–97.2)	92.8 (76.5–99.1)	12.06	0.14	0.89 (0.78–1)
Mild-OST-CD (n = 15) *vs.* PC (n = 28)					
UFC: cutoff > 413 nmol/24 h[a]	60 (32.2–83.6)	0 (0–10.1)[f]	0.6	***	0.54 (0.31–0.78)[h]
Midnight serum cortisol > 207 nmol/liter[c]	80 (51.9–95.6)	64.2 (44–81.3)[f]	2.23	0.31	0.65 (0.46–0.85)[h]
DDAVP test[d]: basal serum cortisol > 331 nmol/liter[e] and Δ-ACTH > 4 pmol/liter[e]	86.6 (59.5–98.3)	92.8 (76.5–99.1)	12.02	0.14	0.90 (0.77–1)
Mild-Cort24-CD (n = 6) *vs.* PC (n = 28)					
UFC: cutoff > 413 nmol/24 h[a]	33.3 (4.3–77.7)	0 (0–10.1)[f]	0.33	***	0.21 (0–0.46)[h]
OST serum cortisol: cutoff > 50 nmol/liter[b]	50 (11.8–88.1)	28.5 (13.2–48.6)[f]	0.69	1.75	0.26 (0–0.55)[h]
OST serum cortisol: cutoff > 138 nmol/liter[b]	16.6 (0.4–64.1)[g]	89.2 (71.7–97.7)	1.53	0.93	0.26 (0–0.55)[h]
DDAVP test[d]: basal serum cortisol > 331 nmol/liter[e] and Δ-ACTH > 4 pmol/liter[e]	100 (60.7–100)	92.8 (76.5–99.1)	13.8	0	0.95 (0.87–1)

a Upper limit of the normal UFC range in our laboratory.
b Cutoff commonly used for CS diagnosis (9).
c Cutoff according to Papanicolaou *et al.* (16).
d CD diagnosis based on the presence of both parameters; absence of either or both excludes CD.
e Cutoff affording the highest sum of SE and SP in combination with the cutoff of the other parameter.

DIAGNOSIS OF ENDOCRINE DISEASE

Differentiation of pathologic/neoplastic hypercortisolism (Cushing's syndrome) from physiologic/non-neoplastic hypercortisolism (formerly known as pseudo-Cushing's syndrome)

European Journal of Endocrinology (2017) **176**, R205–R216

James W Findling[1] and **Hershel Raff**[2]

The most valuable clinical tool for discriminating between physiologic and pathologic Cushing's syndrome is a thorough history and physical examination.

Pseudo-Cushing's diagnoses	Cutoffs/criteria for Cushing's syndrome	Sensitivity	Specificity

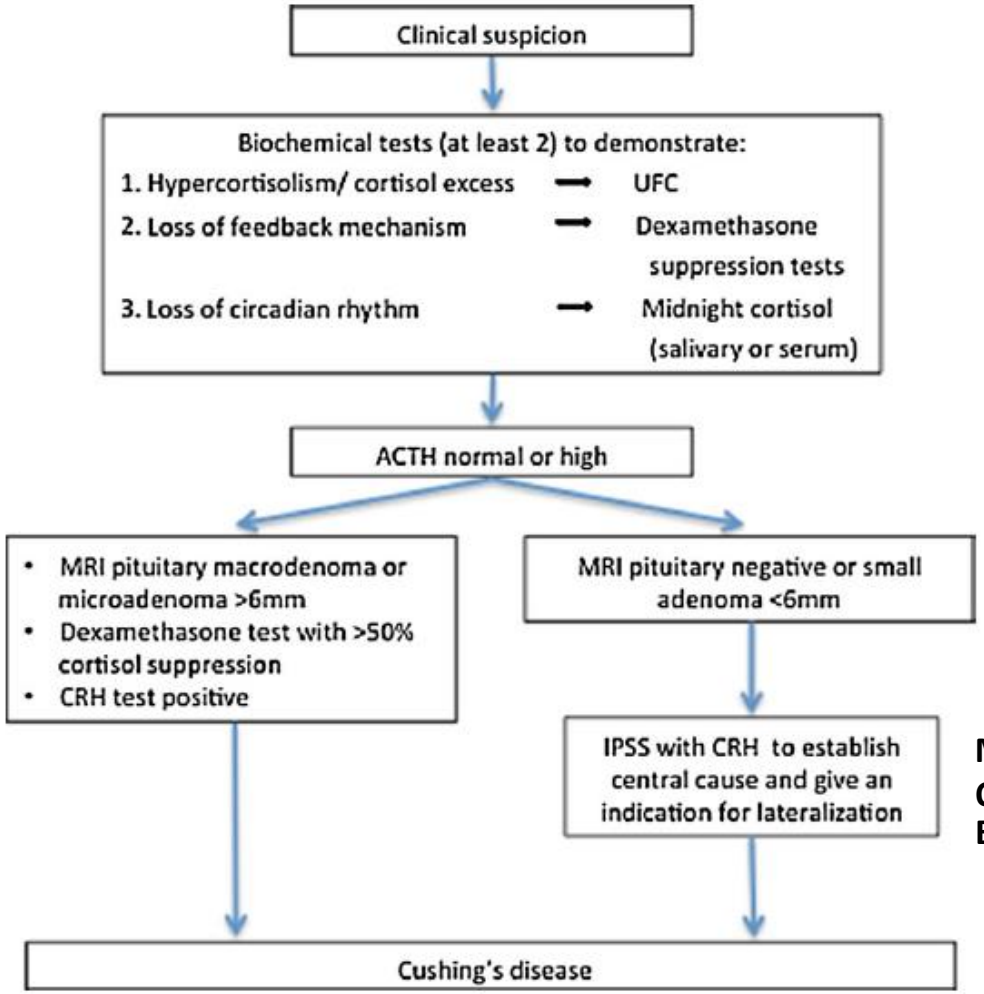
secondary tests such as DDAVP stimulation or dexamethasone–CRH are recommended. Both of these tests seem to perform similarly,

Realtà nella Comunità Endocrinologica Italiana?

Diagnosis of Cushing's disease

Eleni Daniel · John D. C. Newell-Price

Pituitary (2015) 18:206–210



Performance nuove tecniche imaging?

Nuovi cut-off ai tests?

Modalità di esecuzione IPSS?

Quali imaging per la ricerca di EAS?

Fig. 1 Stepwise investigation of suspected Cushing's disease

WORKUP DIAGNOSTICO DELLA SINDROME DI CUSHING …2017…

Il sospetto clinico di CS?

In chi fare screening e come?

Diagnosi nel mild CS?

Quale test per DD Cushing vs Pseudo-Cushing?

Ottimizzazione della DD CD vs EAS?

Quale realtà nella Comunità Endocrinologica Italiana?

L'unione fa la forza...per conoscere…migliorare…

…Grazie… ***a voi e a Valentina D'Angelo***

Characterization of persistent and recurrent Cushing's disease

Nina K. Sundaram · Alessia Carluccio · Eliza B. Geer

Pituitary (2014) 17:381–391

Table 2 Biochemical criteria used to define CD recurrence

References	Biochemical test	Criteria for recurrence
Boggan et al. [76]	Plasma ACTH	Elevated
	Serum cortisol	Elevated
	LDDST	Elevated
Schrell et al. [16]	AM plasma ACTH	>50ρg/ml
	AM serum cortisol	>21μg/dl
	LDDST	Serum cortisol > 2μg/dl
Trainer et al. [25]	AM serum cortisol	>1.8μg/dl
Bochicchio et al. [33]	LDDST	Inappropriate suppression
Sonino et al. [59]	UFC	Elevated
	LDDST	Inappropriate suppression
Blevins et al. [73]	UFC	>120μg/24 h
	LDDST	Inappropriate suppression
Invitti et al. [77]	AM serum cortisol	Elevated
	AM plasma ACTH	Elevated
	UFC	Elevated
Barbetta et al. [74]	UFC	Elevated
	ODST	Inappropriate suppression
Chee et al. [10]	AM and midnight serum cortisol	Elevated
	UFC 1.5 mg	Elevated
	ODST	Serum cortisol >3.6μg/dl
Estrada et al. [11]	UFC	Elevated
	ODST	Serum cortisol >5μg/dl
Rees et al. [22]	AM serum cortisol	>1.8μg/dl
Shimon et al. [17]	UFC	Elevated
	LDDST	>5μg/dl
Yap et al. [23]	UFC	Elevated
	LDDST	Inappropriate suppression
Chen et al. [20]	UFC	Elevated
	8AM and 4PM serum cortisol	Elevated values and lack of diurnal variation
Pereira et al. [12]	ODST (on more than one occasion)	Serum cortisol >3.6μg/dl
	UFC × 2 consecutive samples	Elevated
Hammer et al. 18]	ODST	Serum cortisol ≥5μg/dl
	UFC	Elevated
Valero et al. [14].	UFC	Elevated
	Plasma ACTH	High or normal
	Serum cortisol	High
	Midnight serum cortisol	>1.8 μg/dl
	ODST	Serum cortisol >1.8 μg/dl
Rollin et al. [75]	ODST	Serum cortisol >3μg/dl
Atkinson et al. [19]	UFC	Elevated
	LDDST	Inappropriate suppression
Esposito et al. [21]	Serum cortisol	>25μg/dl
Carrasco et al. [13]	UFC	>90μg/24 h
	ODST	>1.8μg/dl
	Midnight serum cortisol	>7.5μg/dl
Salem et al. [15]	LDDST	Serum cortisol >1.8μg/dl

Units were converted to μg/24 h for UFC and μg/dl for serum cortisol

UFC, 24-hour urinary free cortisol; ACTH, adrenocorticotropic hormone; LDDST, low dose dexamethasone suppression test; ODST, 1 mg overnight dexamethasone suppression test

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4.4 We recommend using tests to screen for hypercortisolism to assess for recurrence in patients with ACTH-dependent CS. (1|⊕⊕⊕○)