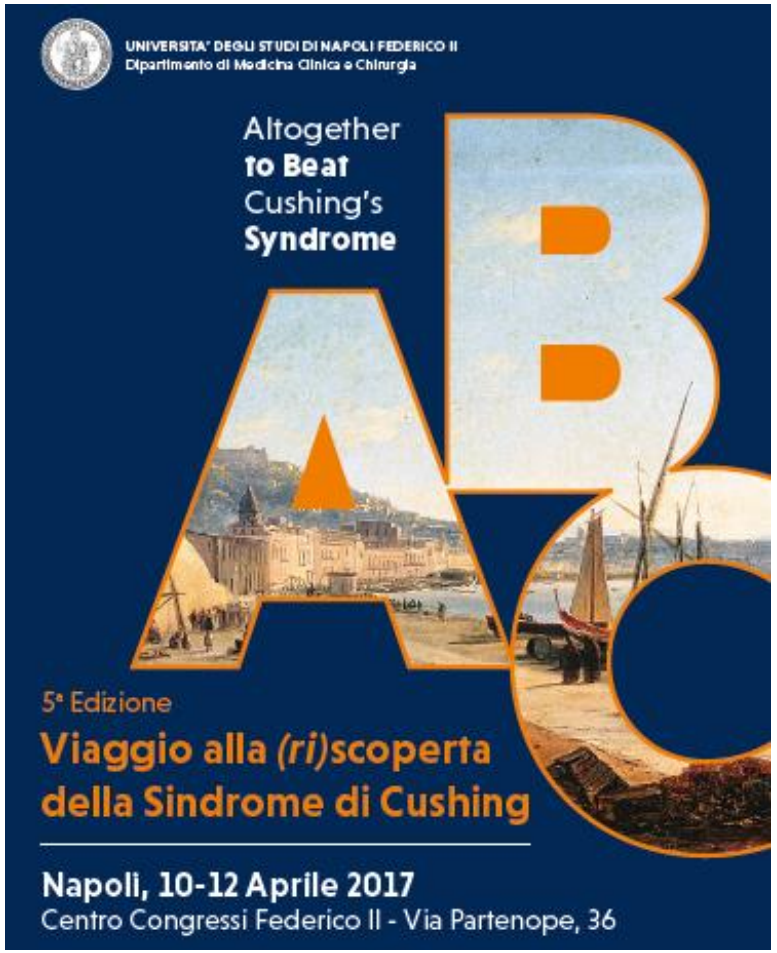

AZIENDA OSPEDALIERA UNIVERSITA' PADOVA

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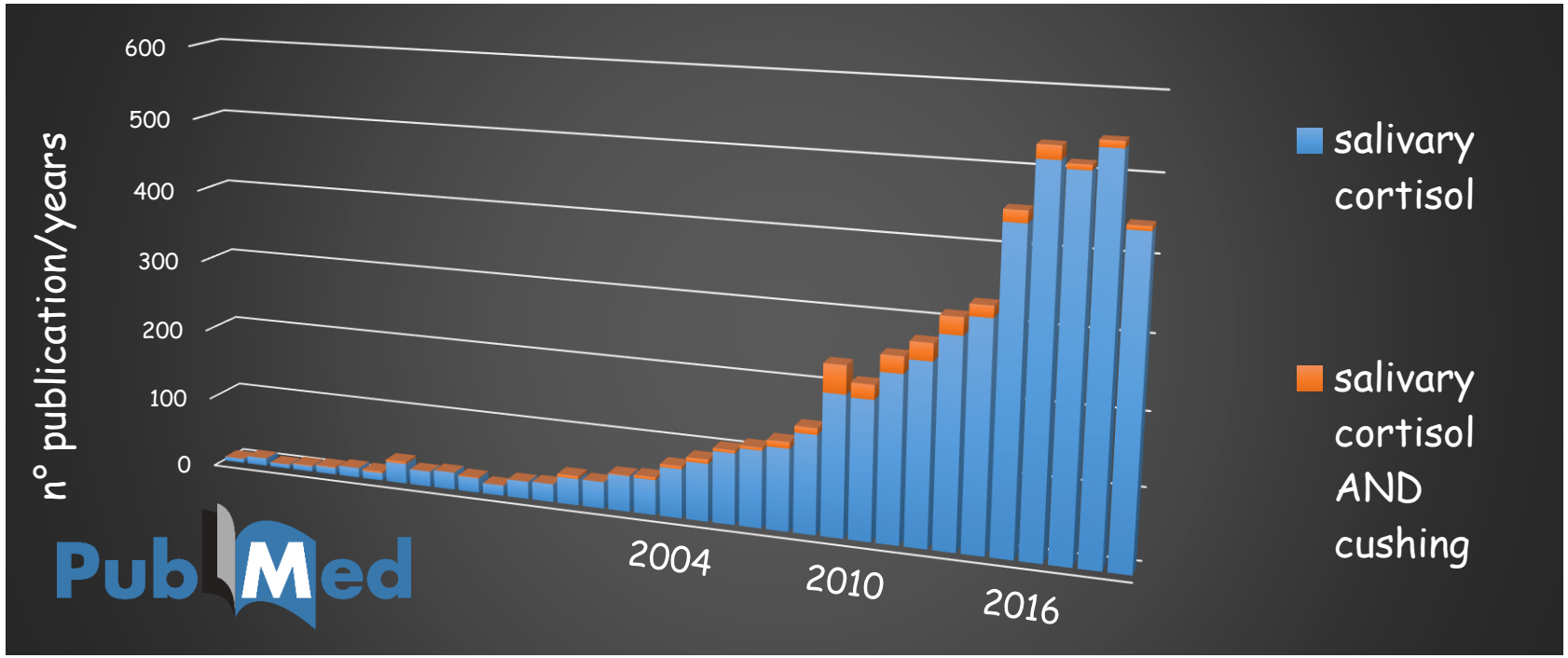
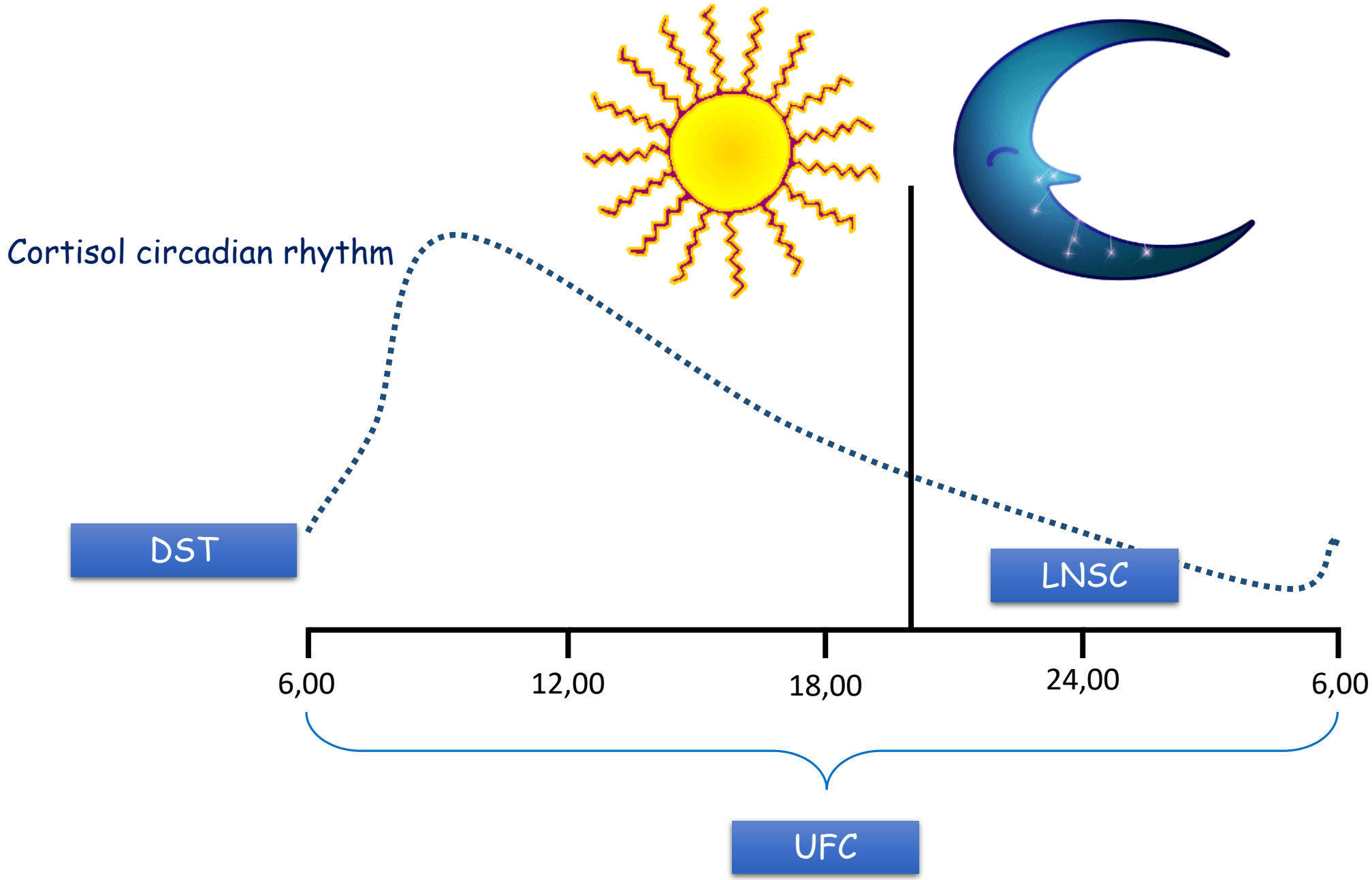
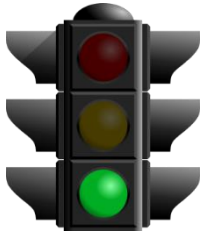
Endo-ERN

Do not forget salivary cortisol!!!!!!!!!!!!!!!!!!!!!



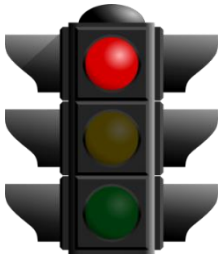

Cortisol circadian rhythm
DST
LNSC
6,00
12,00
18,00
24,00
6,00
UFC

Overnight 1-mg DST



PROs

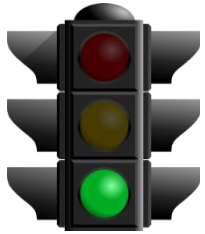
- Large studies
- Subclinical hypercortisolism



CONs

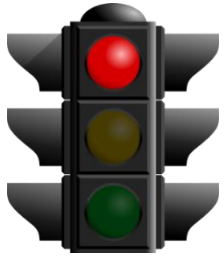
- DEX absorption and metabolism (P450 enzyme system)
- Patient instruction
- Poor sleep, aging
- Cortisol assays

LNSC



PROs

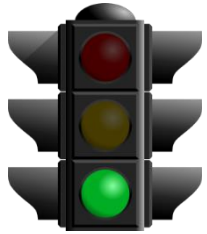
- Stress-free & outpatient
- Easy to use
- Elevated diagnostic accuracy
- Cyclical , recurrent CS/CD



CONs

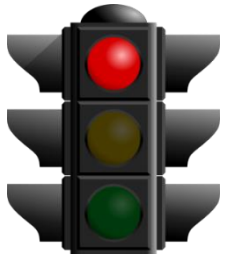
- Immunoassays ➔ validation
- Acid or sugar Food, licorice, smoke
- Oral GC
- Lack of widespread use

UFC



PROs

- 24h integrated measurement
- Free hormone
- Used in many centers



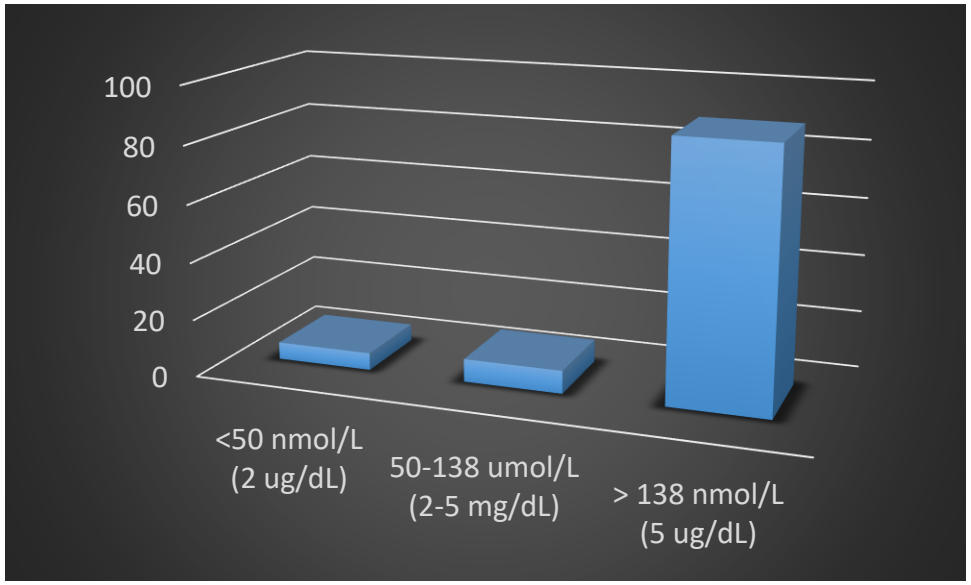
CONs

- 24 h collections
- ! Renal function
- Day to day variability
- Assay (RIA and ELISA)

DST: rischio di falsi negativi

The Low-Dose Dexamethasone Suppression Test: A Reevaluation in Patients with Cushing's Syndrome

103 CS



DST open issues

- Dexamethasone metabolism
- Adrenal incidentaloma (up to 8-10% of population)
  ➔ threshold 138 nmol/L to consider autonomous cortisol secretion

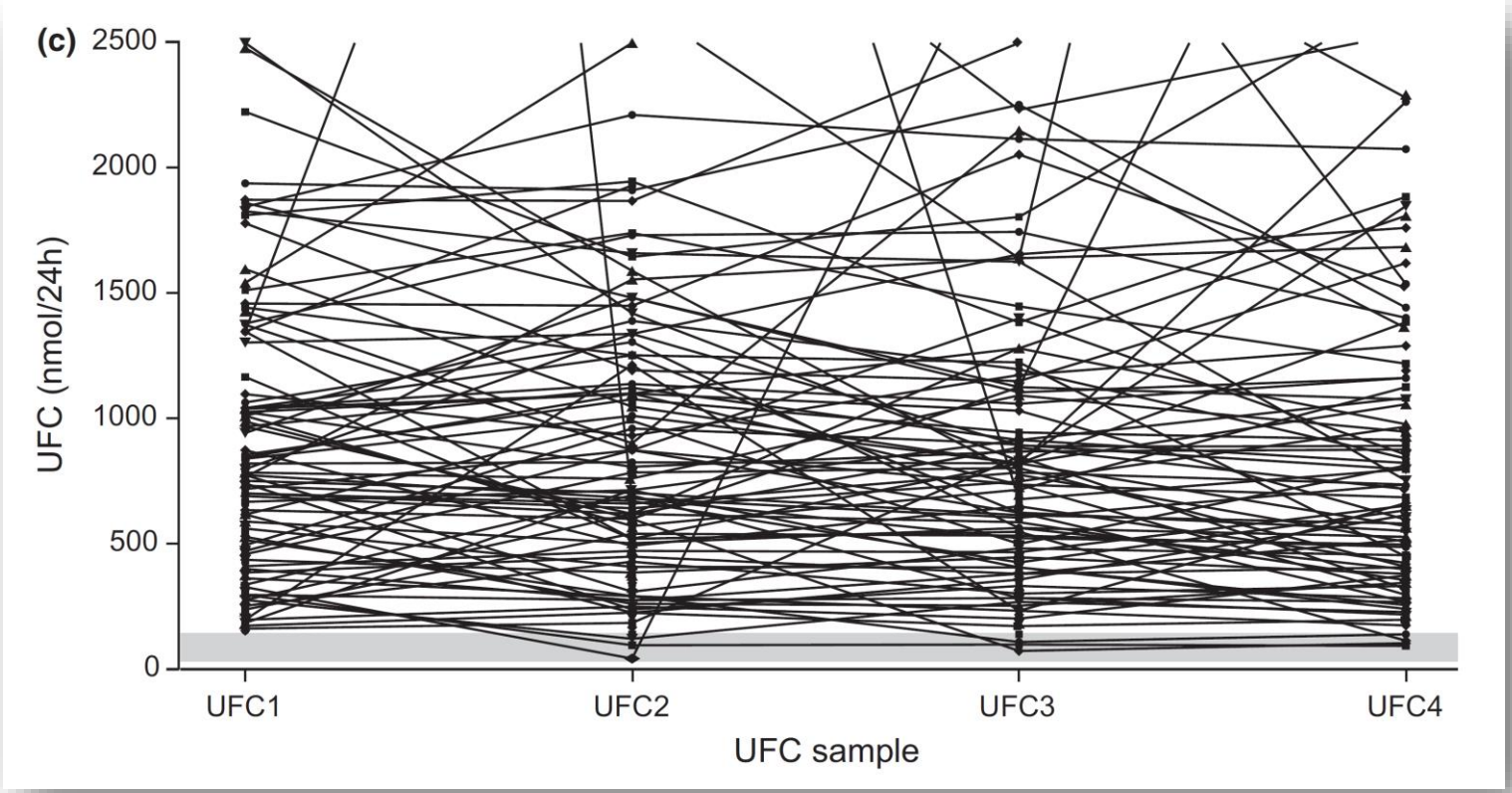
14 patients cortisol after 1 mg DST < 138 nmol/L
6 patients cortisol after 1 mg DST < 50 nmol/L ➔ BUT positive ACTH pituitary adenoma!!!!!!!!!!!!!!!!!!!!!

Findling JW, J Clin Endocrinol Metab, 2004

UFC: ampia variabilità → rischio falsi negativi

High variability in baseline urinary free cortisol values in patients with Cushing's disease

- 152 with persistent/recurrent or de novo CD
- mean UFC ≥1.5 ULN
- 4 baseline urine collections



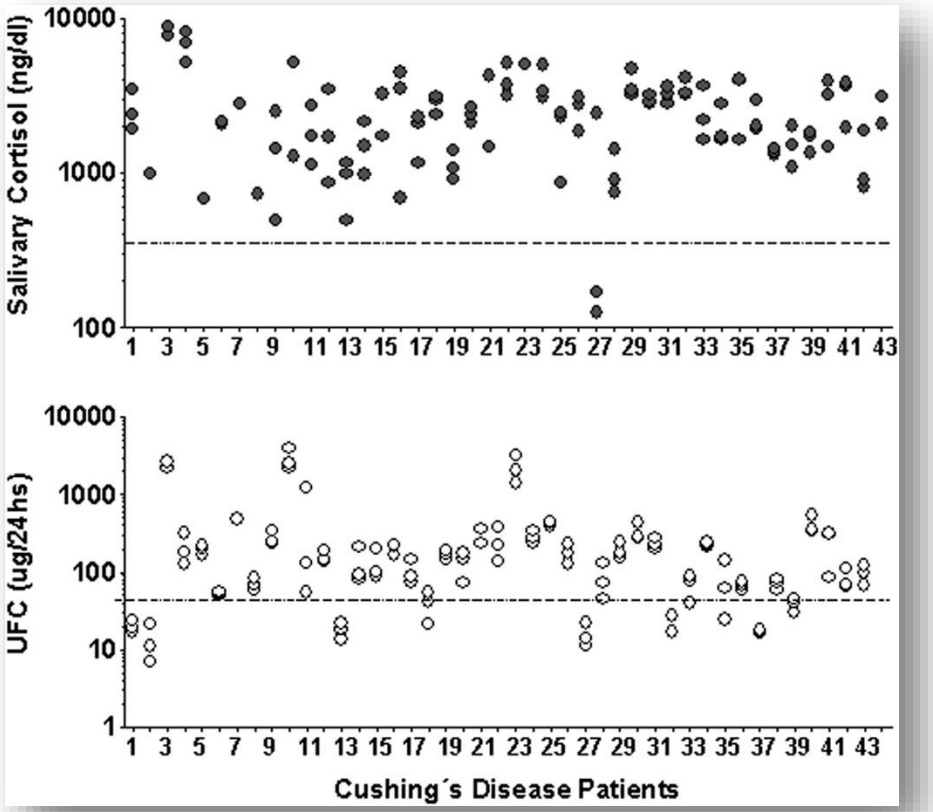
7 patients with at least
1 normal UFC
(but mean >1.5 UFC)

Petersenn S, Clin Endocrinol, 2013

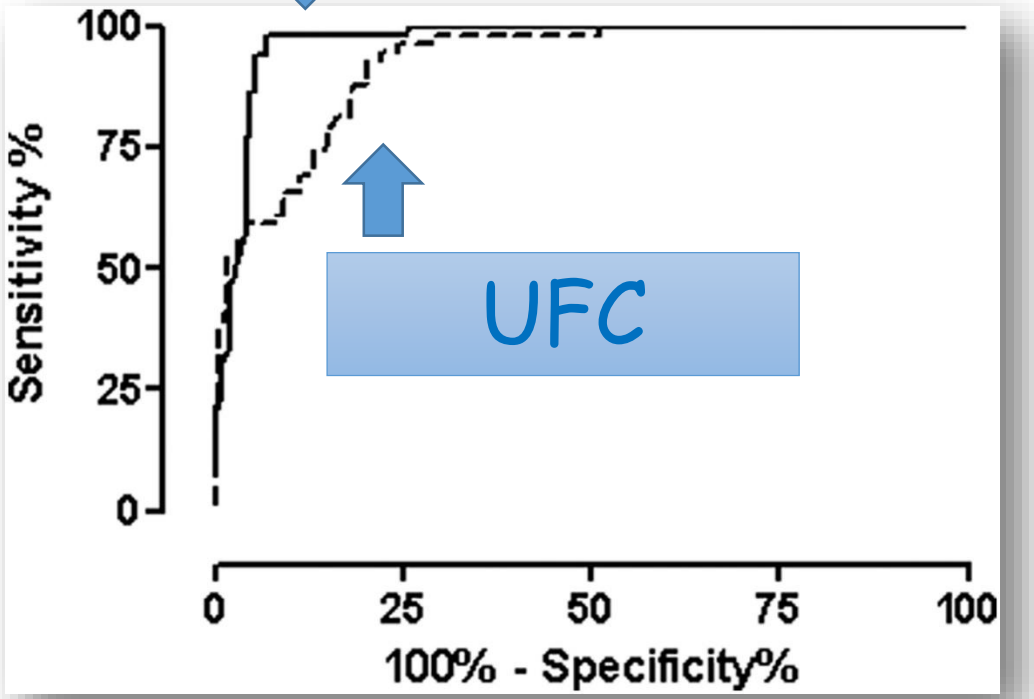
LNSC vs UFC

Late-night Salivary Cortisol Has a Better Performance Than Urinary Free Cortisol in the Diagnosis of Cushing's Syndrome

- 52 CS
- 18 obese



LNSC



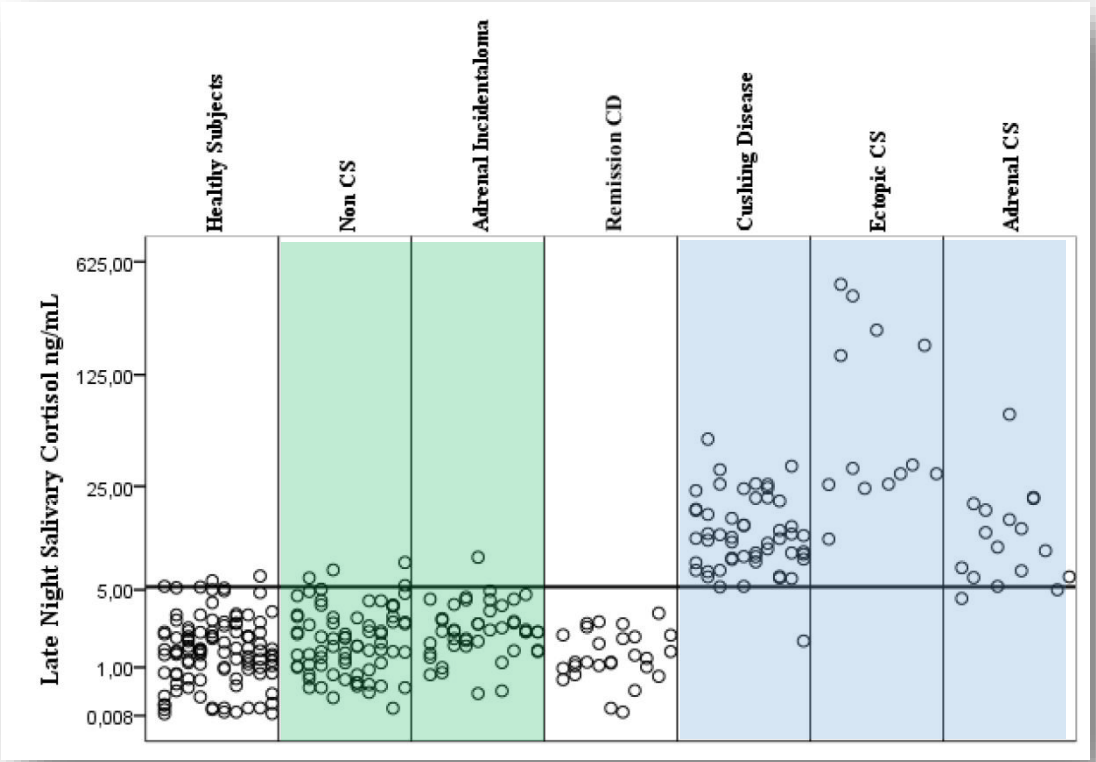
UFC

Elias PCL, *J Clin Endocrinol Metab*, 2013

LNSC: evidence

Performance of salivary cortisol in the diagnosis of Cushing's syndrome, adrenal incidentaloma, and adrenal insufficiency

- 104 healthy controls
- 73 suspected CS
- 27 remission CS
- 45 non cortisol secreting adrenal adenoma
- 82 CS



Population	LNSC ng/mL	SE %	SP %	AUC
CS vs healthy subjects	5.24	96.3	97.1	0.992
CD vs healthy subjects	5.24	98.1	97.1	0.991
CS vs non-CS	5.15	96.3	94.5	0.986
CD vs non-CS	5.15	98.1	96.5	0.984
CD recurrence vs non-CS	5.15	100	95.5	0.987
CS vs adrenal incidentaloma	4.95	97.6	97.8	0.985

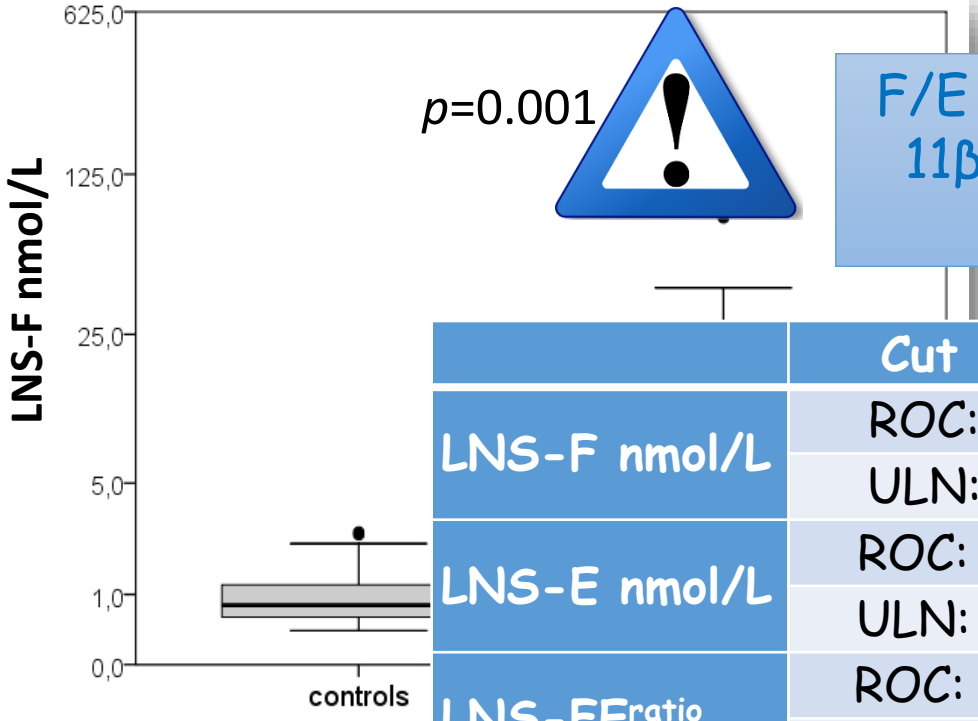
RIA assay!

Ceccato F, Eur J Endocrinol, 2013

LNSC: evidence

Salivary cortisol and cortisone by LC–MS/MS: validation, reference intervals and diagnostic accuracy in Cushing's syndrome

- 91 healthy controls
- 25 CS



F/E < 1 due to conversion by 11βHSD type 2 present in salivary glands

HPLC
Agilent 1100

MS/MS
Agilent 6430

	Cut off	SE%		
LNS-F nmol/L	ROC: 2.4	100.0		
	ULN: 2.5	96.0		
LNS-E nmol/L	ROC: 14.2	100.0	98.9	
	ULN: 13.0	100.0	97.8	
LNS-FE^{ratio}	ROC: 0.23	76.0	66.3	0.761
	ULN: 0.37	24.0	97.8	

Specificity

Antonelli G, Clin Chim Acta. 2015

UFC: evidence (still?)

Is urinary free cortisol of value in the diagnosis of Cushing's syndrome?

+ methodological difficulties in 24-h urine collection
+ assay precision
+ increased prevalence of mild, preclinical or cyclic CS +
SE and SP UFC are less than ideal

= we suggest the use of other more novel tests (LNSC)

Alexandraki KI, Curr Opin Endocrinol Diabetes Obes, 2011

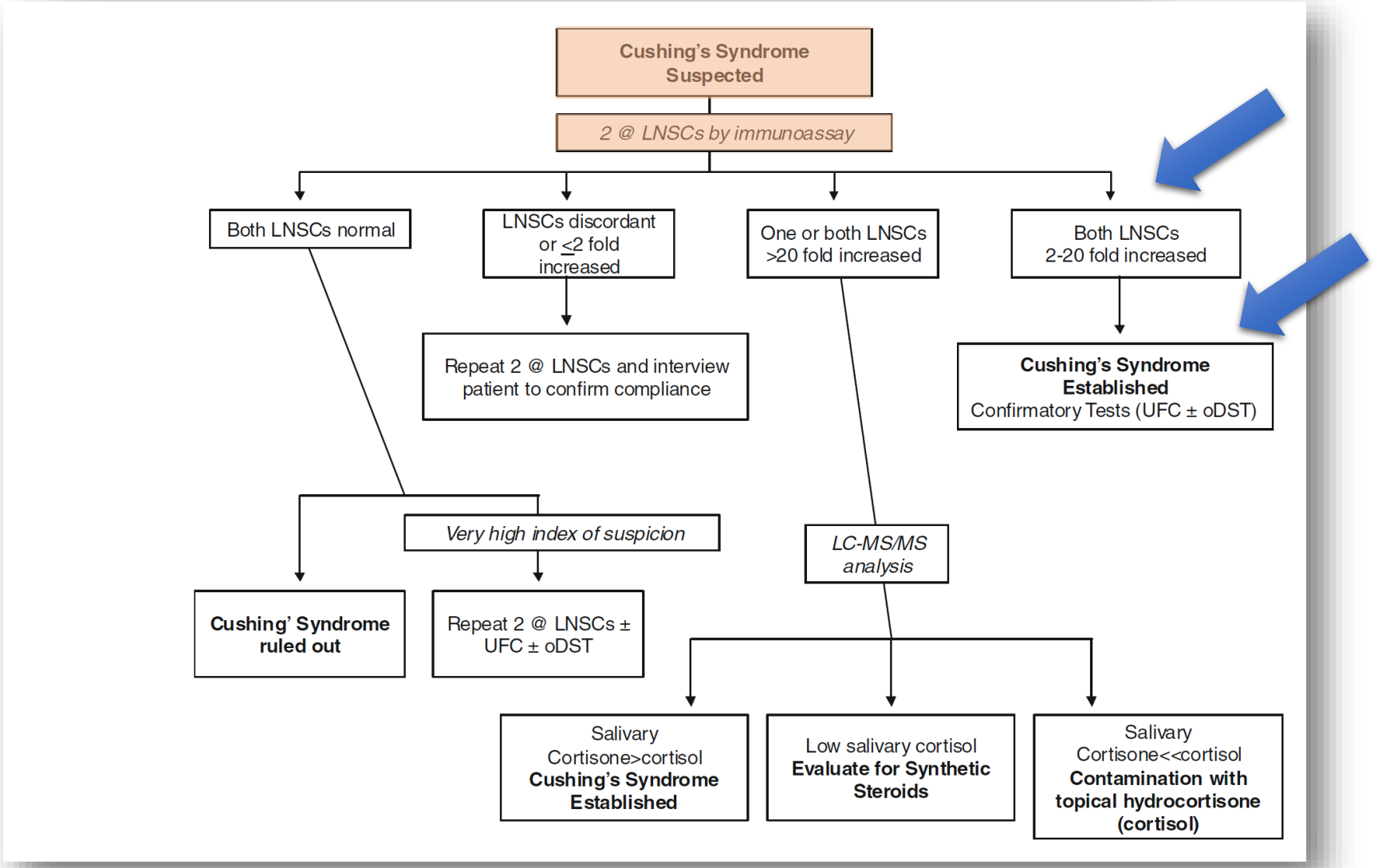
Urine Free Cortisol in the Diagnosis of Cushing's Syndrome: Is It Worth Doing and, If So, How?

1ST QUESTION: does the measurement of UFC have adequate diagnostic sensitivity and specificity to be a useful test?

Only in hypercortisolism, since free cortisol appears in urine only when its concentration exceeds the binding capacity of CBG and albumin

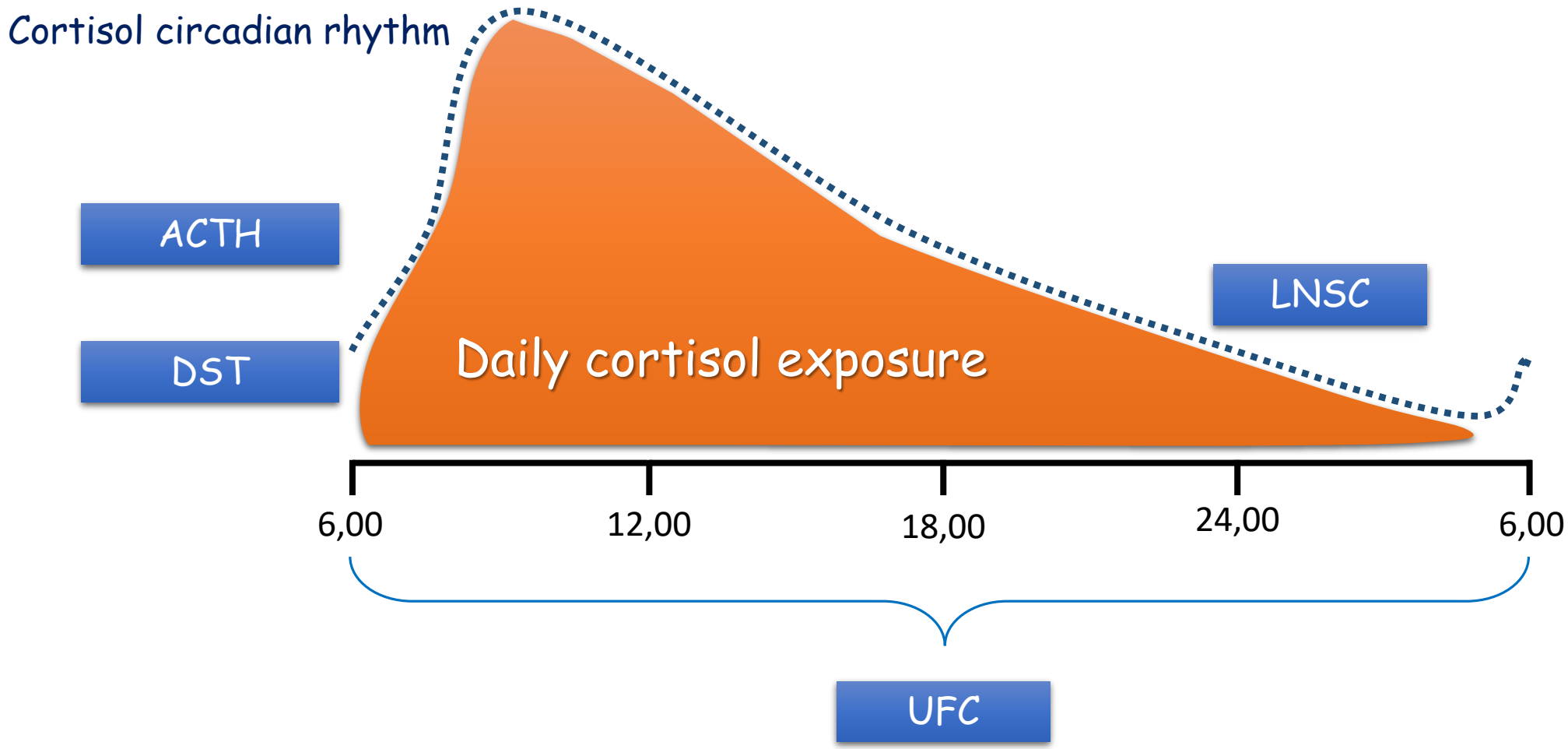
Raff H, J Clin Endocrinol Metab, 2015

Cushing's syndrome: diagnosis and surveillance cortisol



Raff H, Pituitary 2012

Is there something new?



Ruolo “Complementare” dei tests di screening nel sospetto di CS

➢ GRAVIDANZA/ EstroProgestinici	➡	**UFC, cortisolo salivare notturno**
	⛔	**DST test**
➢ TERAPIA ANTI-EPILETTICA	➡	**UFC,Cortisolo salivare notturno,**
	⛔	**DST test**
➢ INSUFFICIENZA RENALE	➡	**Cortisolo salivare notturno**
	⛔	**UFC, DST test**
➢ S. CUSHING ciclica o recidiva CD	➡	**Cortisolo salivare notturno**
	⛔	**DST test**
➢ INCIDENTALOMA	➡	**DST**
	⛔	**UFC, cortisolo salivare notturno**

Mattia Barbot

Filippo Ceccato

Nora Albiger

Marialuisa Zilio

Laura Lizzul

Daniela Regazzo

Gianluca Occhi

Andrea Daniele

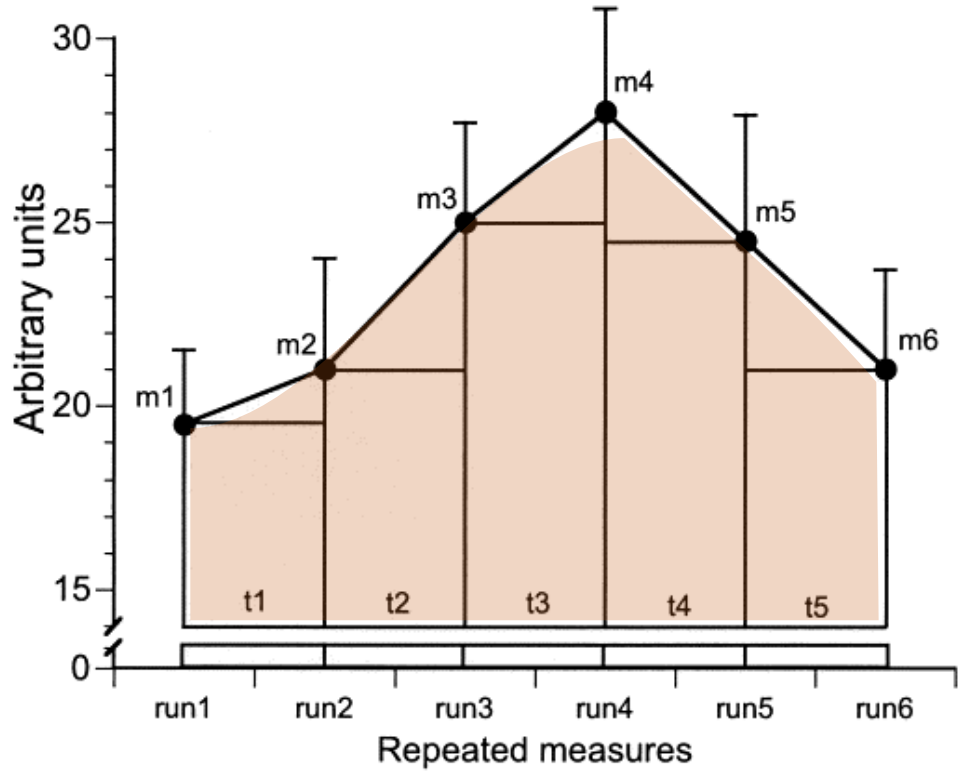
Open issues

- LNSC: 1 or 2 collections?
- High clinical suspicion and normal LNSC: repeat LNSC or use other tests?
- Elevated LNSC (2-20 times ULN): sufficient for CS diagnosis ? Other tests to confirm?
- 2 LNSC discordant determinations: what we have to do?
- Possible LNSC contamination if LNSC >20 ULN ? Which other study?
- Immunoassay or MS/MS? Is it ncessary only one, are necessary both?

Daily (salivary) cortisol exposure

Daily cortisol exposure

AUC (area under the curve) of salivary cortisol concentration from the 6 collections



$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i)}{2}$$