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IL WORK-UP DIAGNOSTICO: ACTH-TEST DOSI STANDARD VERSUS BASSE DOSI

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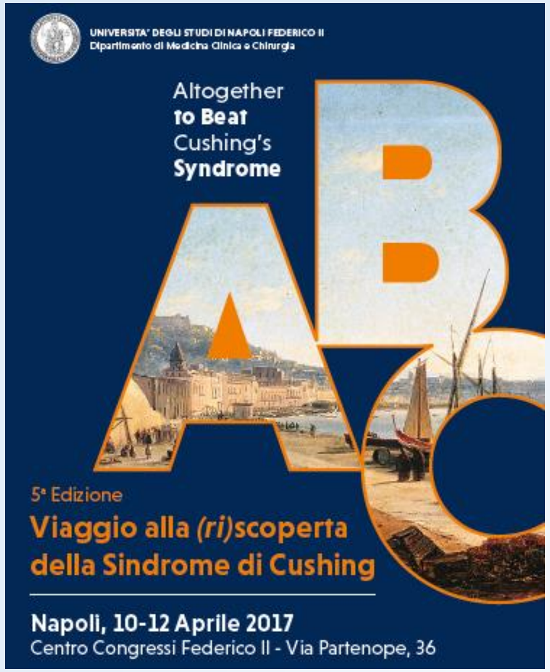
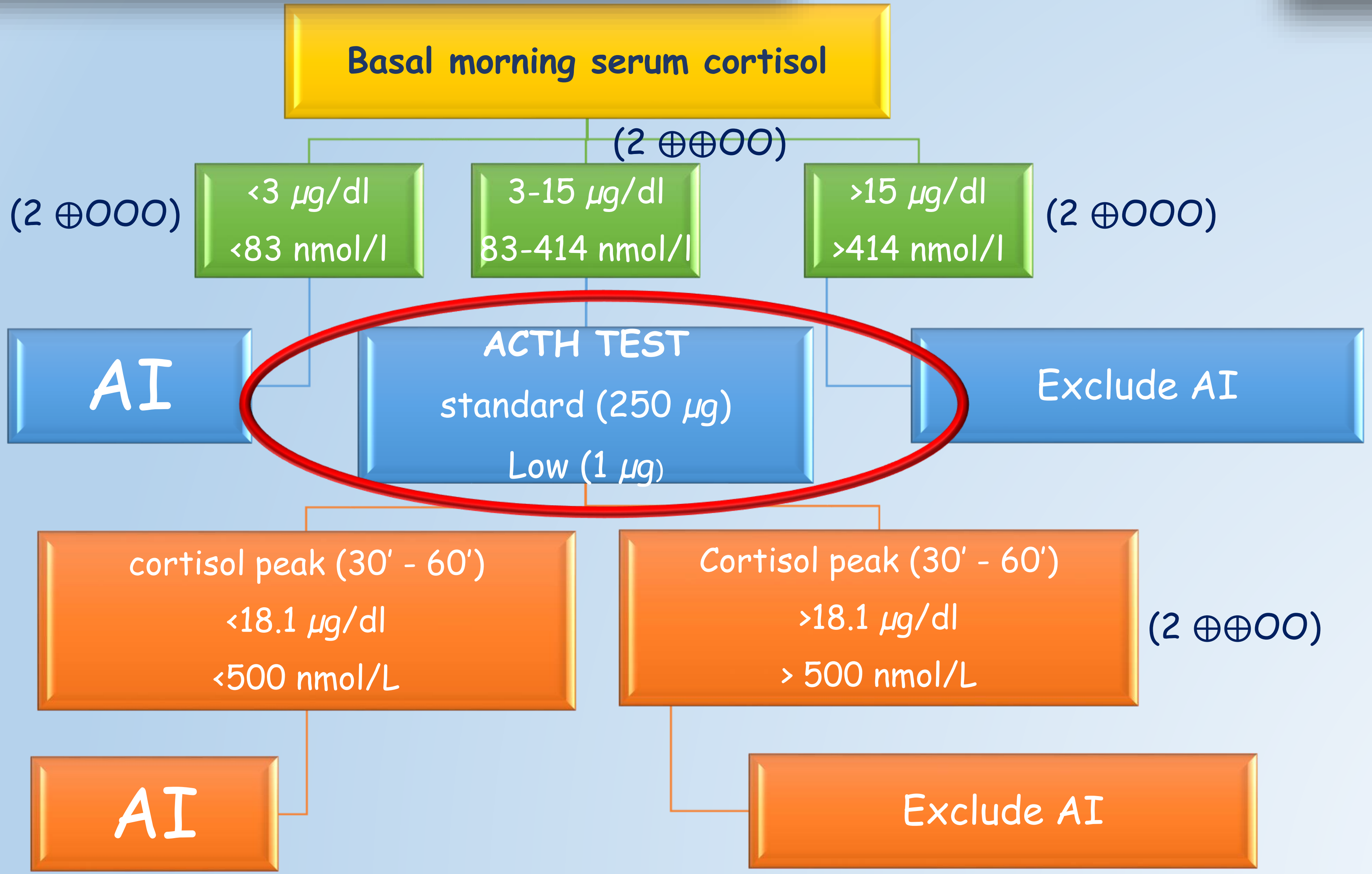
Endo-ERN



Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline

ENDOCRINE SOCIETY



Fleseriu JCEM 2016

Secondary adrenal insufficiency: other tests

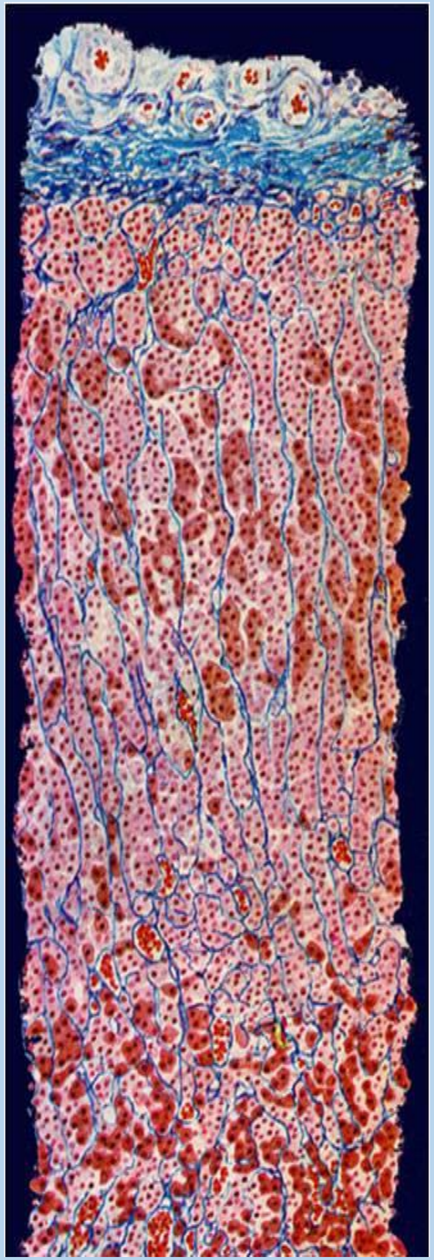
- Insulin tolerance test
- Metyrapone test
- CRH TEST

Why 2 tests?

Why an ACTH dose of 250 μg became the standard in clinical practice when far lower doses were known to stimulate maximally the adrenal cortex is somewhat a mystery.

Tordjman, Clin Endo, 2000

ACTH test(S)

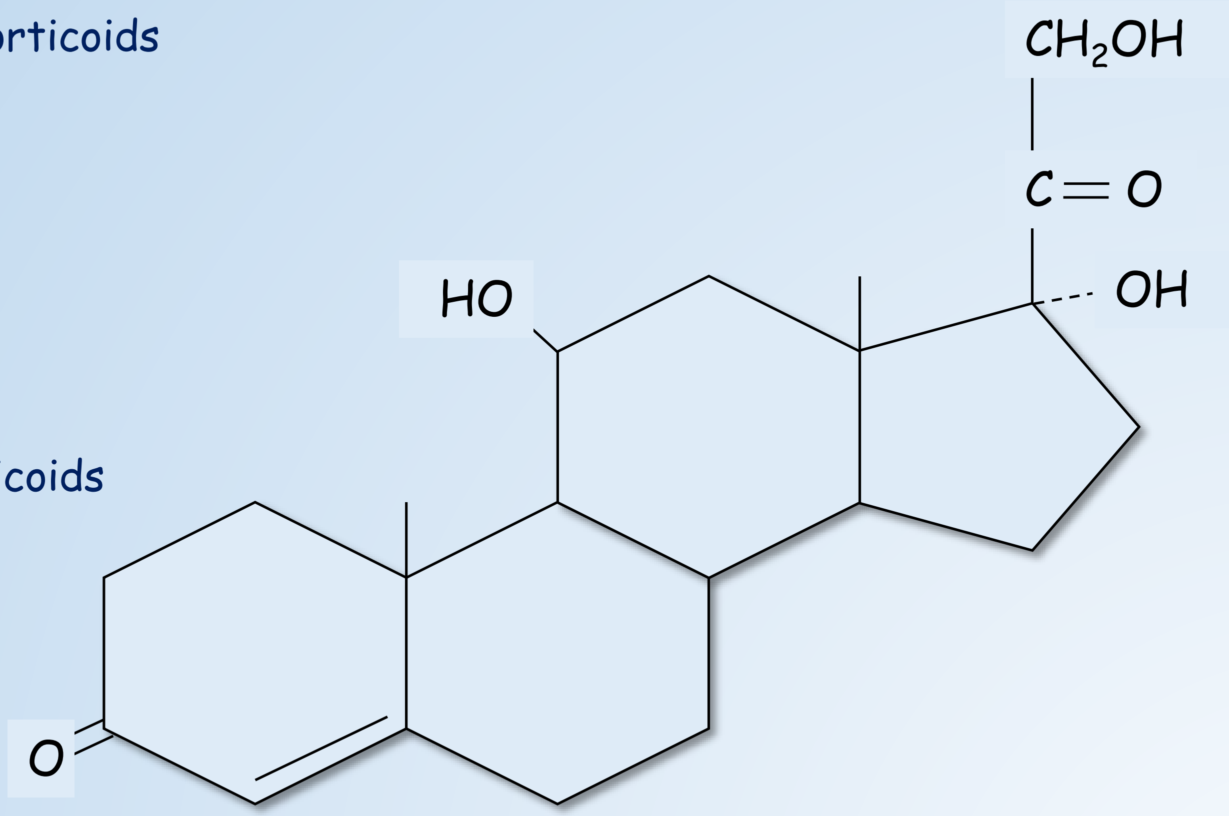


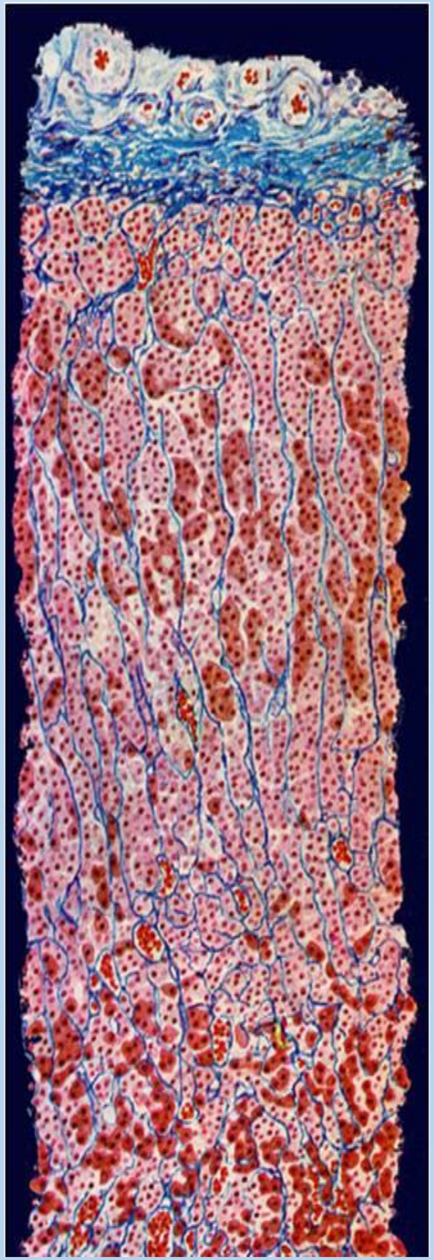
WHY: during chronic ACTH deficiency adrenals (zona fasciculata) present a reduced response to ACTH

Zona glomerulosa ➔ mineralcorticoids

Zona fascicolata ➔ glucocorticoids

Zona reticularis ➔ androgens



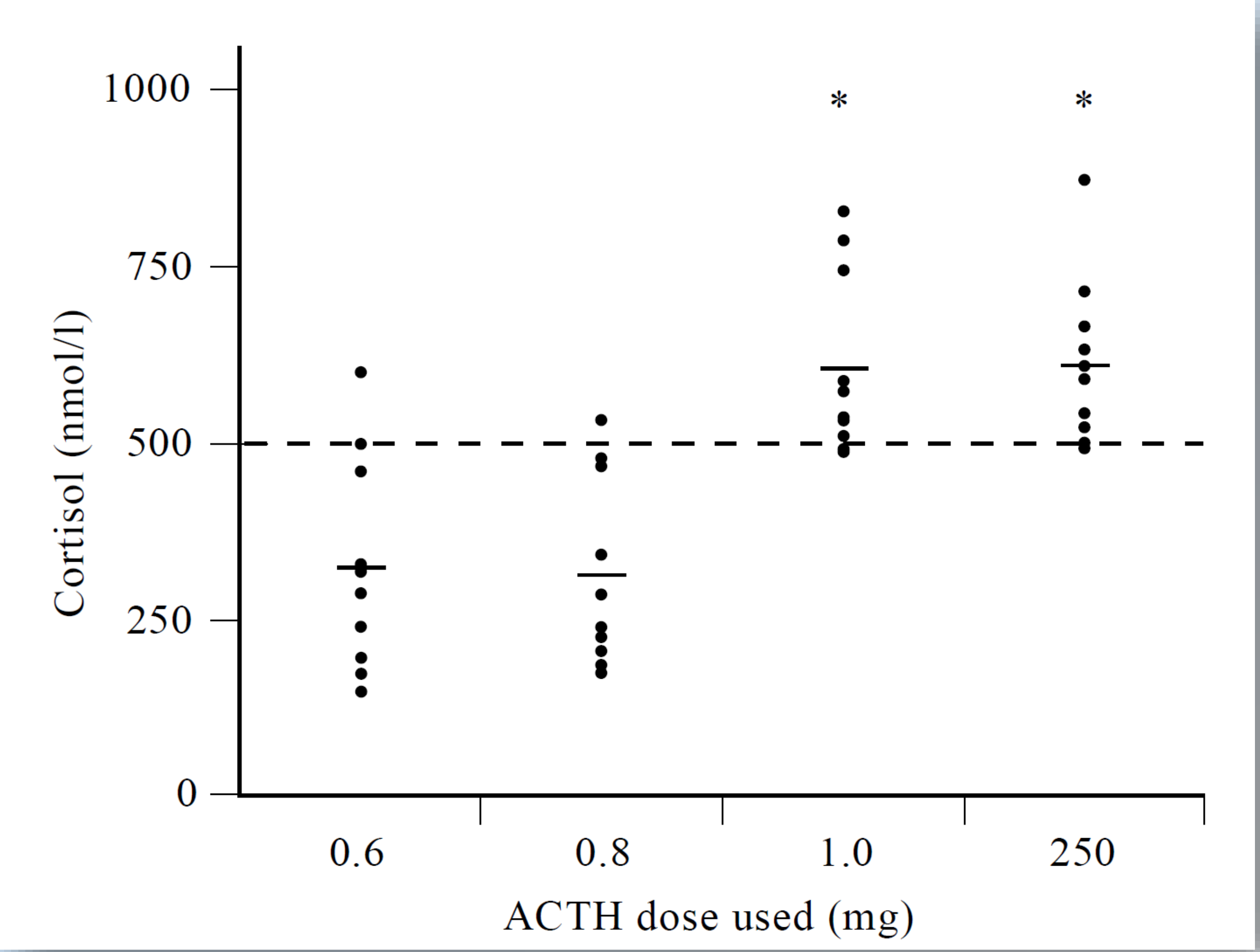


250 µg

1 µg

One microgram is the lowest ACTH dose to cause a maximal cortisol response. There is no diurnal variation of cortisol response to submaximal ACTH stimulation

- ✓ Ten normal volunteers (5 ♀)
- ✓ Aged 20-56 years
- ✓ Low and standard dose
- ✓ Suppression with 1 mg dex



Gabriel Dickstein, EJE 1997

250 vs 1 μg

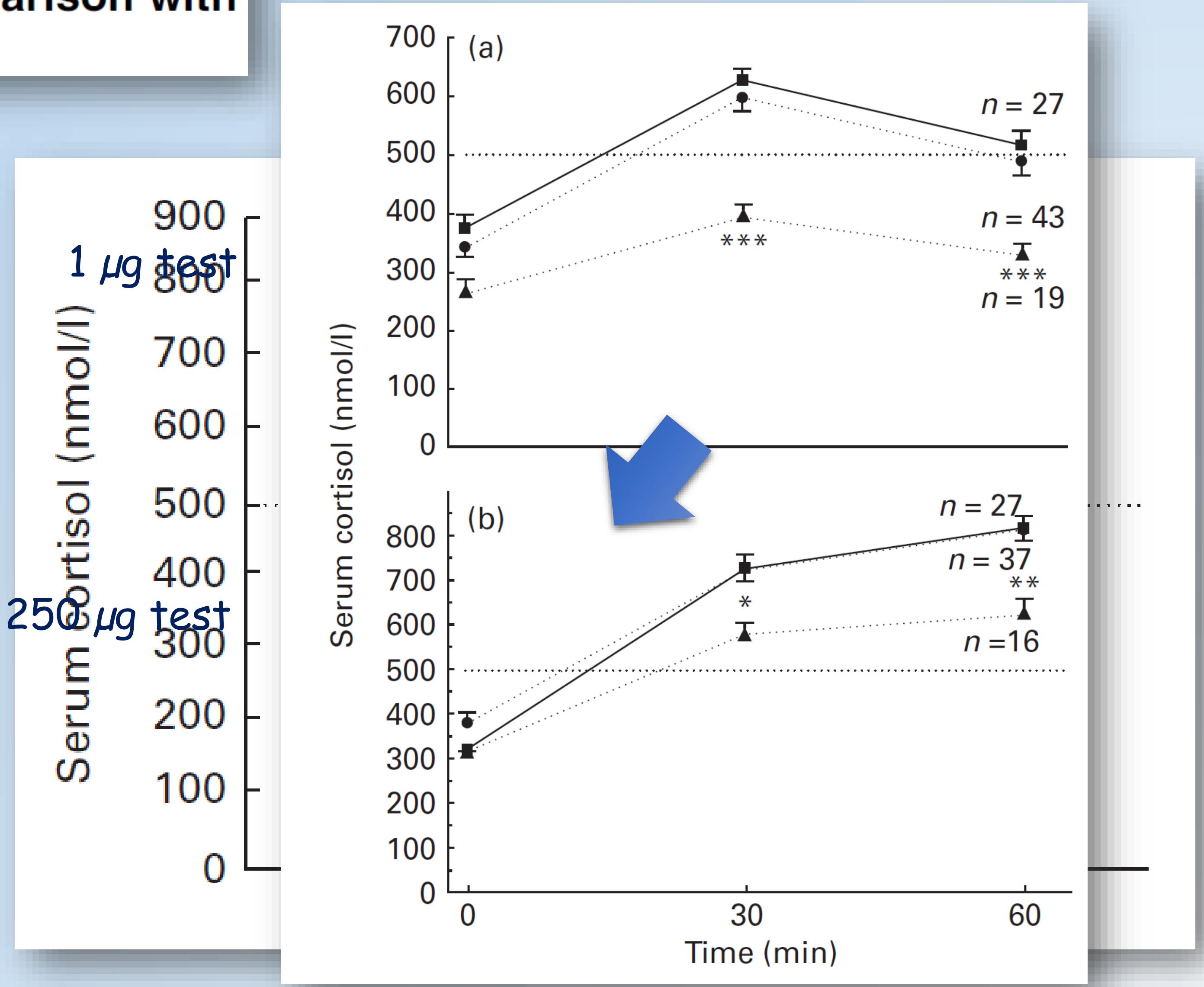
Low-dose (1 μg) adrenocorticotrophin (ACTH) stimulation as a screening test for impaired hypothalamo–pituitary–adrenal axis function: sensitivity, specificity and accuracy in comparison with the high-dose (250 μg) test

27 healthy

43 pituitary disease and normal HPA

19 pituitary diseases and impaired HPA

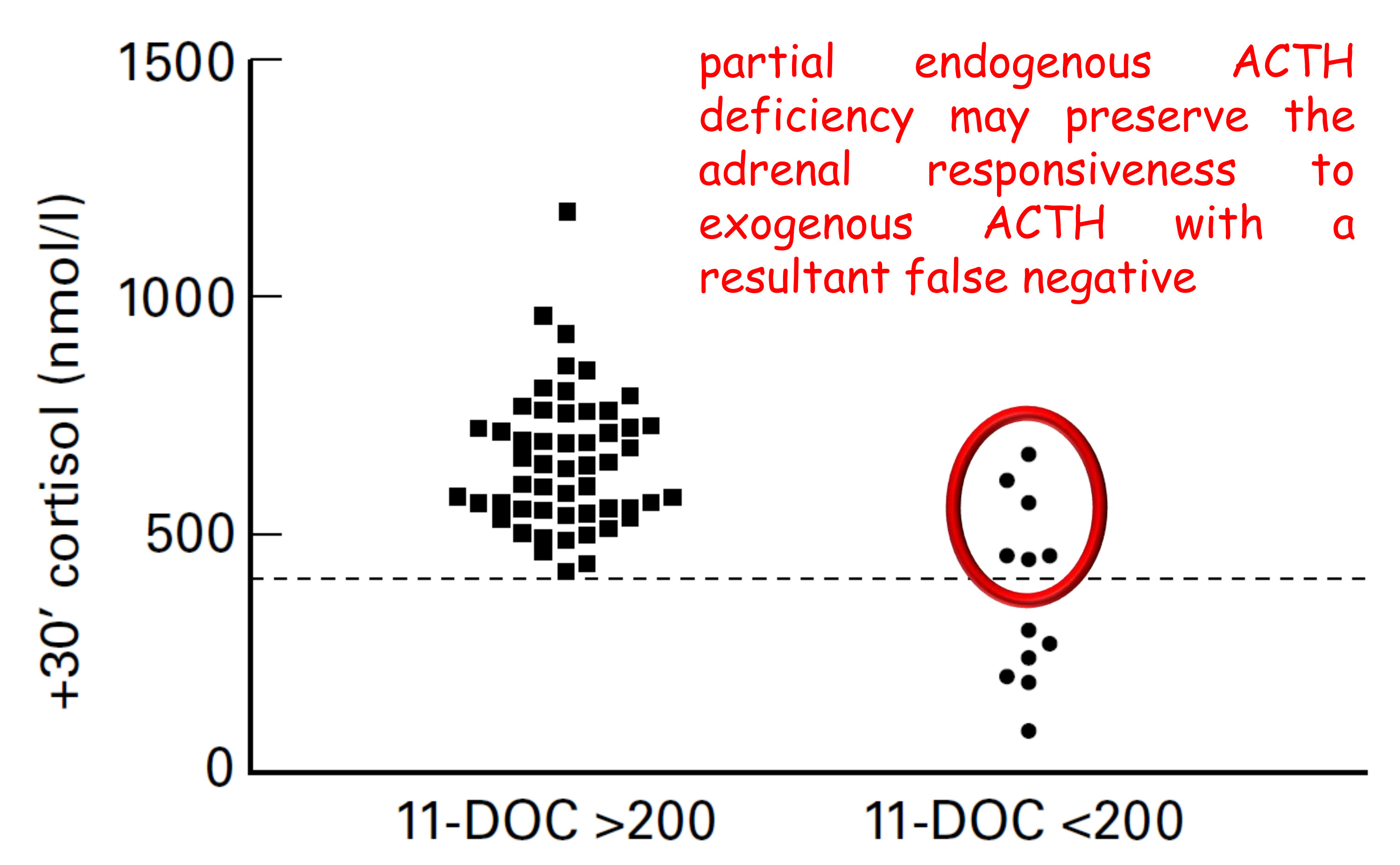
1 and 250 µg test



Tordjman, Clinical Endocrinology 2000

The low dose ACTH stimulation test is less sensitive than the overnight metyrapone test for the diagnosis of secondary hypoadrenalism

- ✓ 21 normal subjects
- ✓ 65 pituitary disease

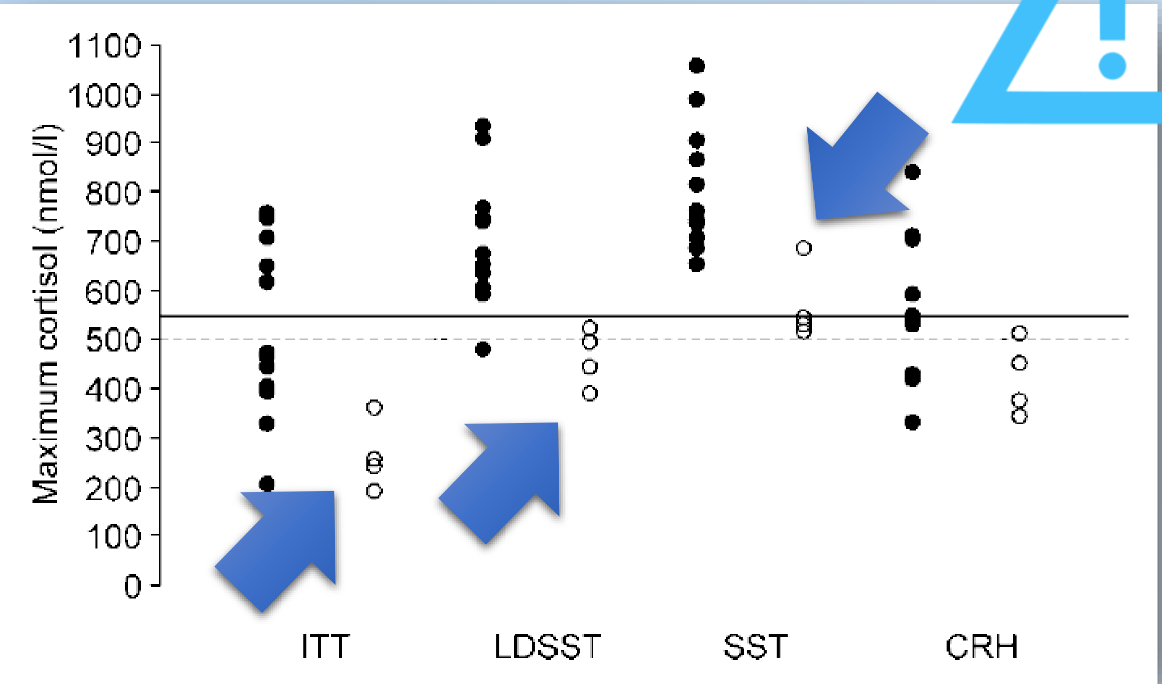


- ✓ 2 groups: normal (11-deoxycortisol > 200 nmol/l) and subnormal ACTH secretory status with metyrpone test

Soule, Clinical Endocrinology 2000

Evaluation of adrenal function in patients with growth hormone deficiency and hypothalamic–pituitary disorders: comparison between insulin-induced hypoglycemia, low-dose ACTH, standard ACTH and CRH stimulation tests

✓ 24 known GHD and pituitary disease



○ Overt SAI

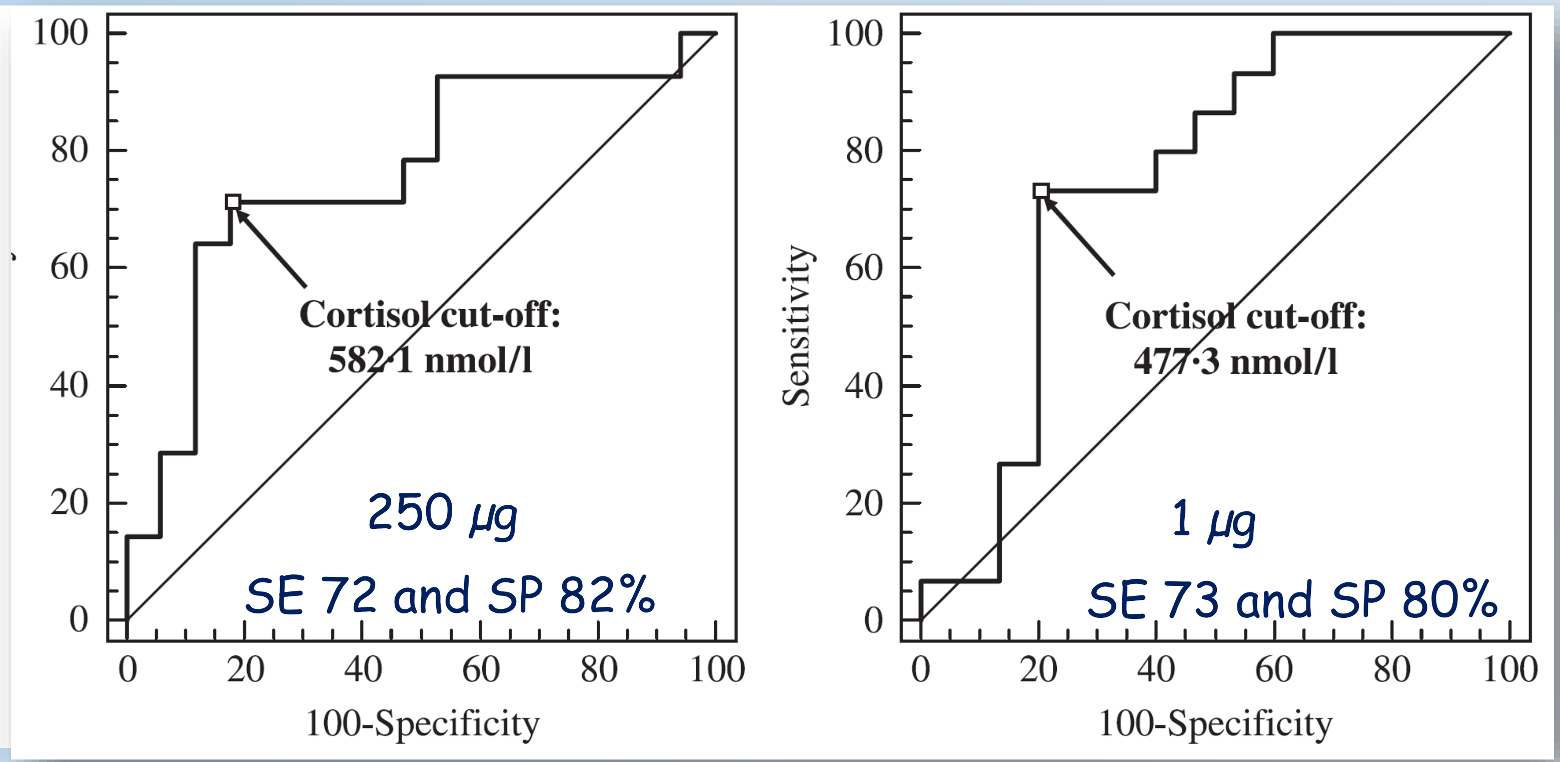
● normal

...none of these tests can be considered completely reliable for SAI...consequently, **clinical judgment remains one of the most important issues**

Maghnie, EJE 2005

Hypothalamus–pituitary–adrenal axis evaluation in patients with hypothalamo–pituitary disorders: comparison of different provocative tests

- ✓ 31 patients with HPA disorders and normal basal cortisol
- ✓ ITT reference test
- ✓ Metyrapone test
- ✓ ACTH test: 250, 1 and 0.06 μg

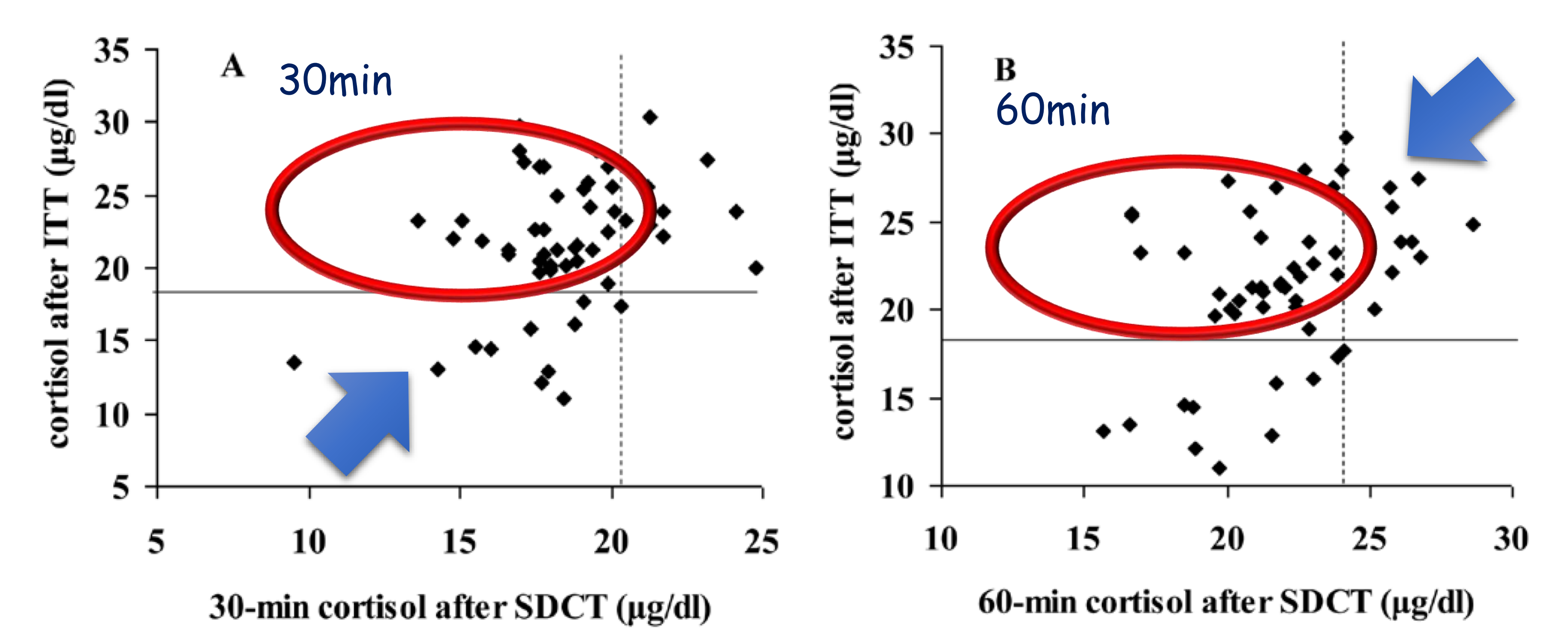


neither MET nor ACTH test can be considered completely reliable for the diagnosis of SAI, when compared with ITT that remains the best test…

Giordano, Clinical Endocrinology 2008

Is the 250 μg ACTH test a useful tool for the diagnosis of central hypoadrenalism in adult patients with pituitary disorders?

- ✓ 55 patients with HPA disorders
- ✓ ITT Metyrapone test
- ✓ 250μg ACTH test



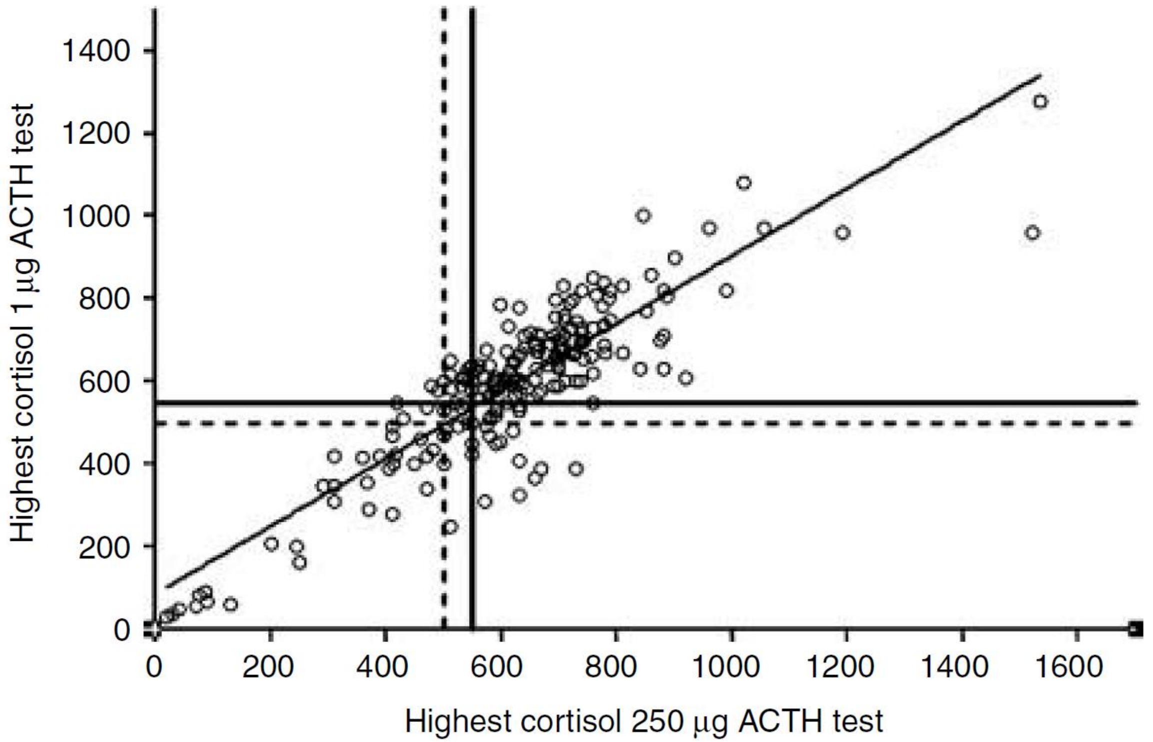
SDCT is not a reliable tool to identify HPAI, but it appears to be more useful in confirming the normality of HPA

Ferrante, Hormones 2012

CLINICAL STUDY

Comparison of the cortisol responses to testing with two doses of ACTH in patients with suspected adrenal insufficiency

- ✓ both 1 μg ACTH test and a 250 μg
- ✓ 207 patients (109 suspected secondary AI)
- ✓ maximum 6 weeks between both tests
- ✓ 3 months after surgery



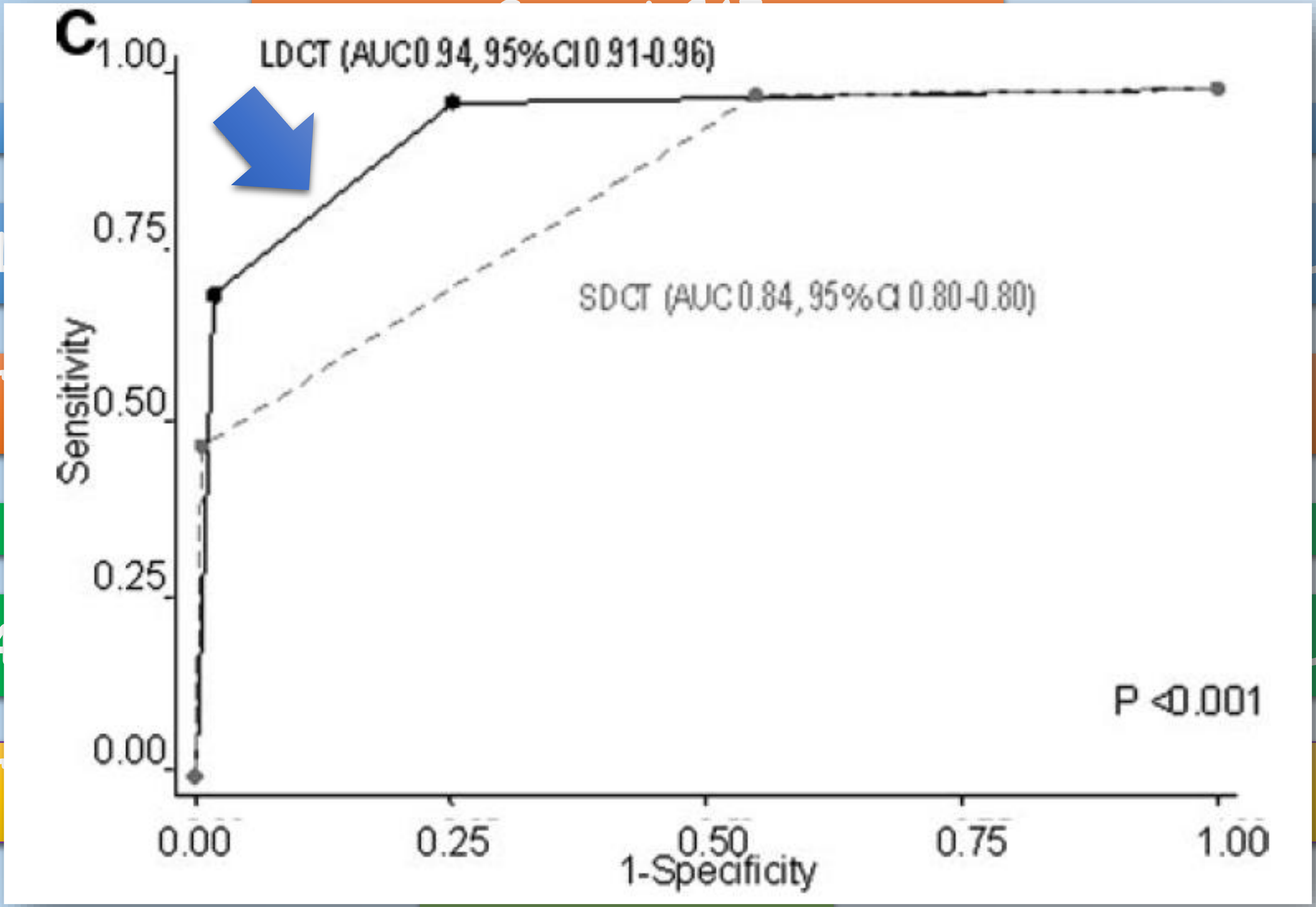
The mean maximal cortisol response @30 min

- ✓ 596 nmol/l for the 1 μg test
- ✓ 622 for the 250 μg test

Dekkers, EJE, 2011

Corticotropin Tests for Hypothalamic-Pituitary-Adrenal Insufficiency: A Metaanalysis

13 studies
679 patients

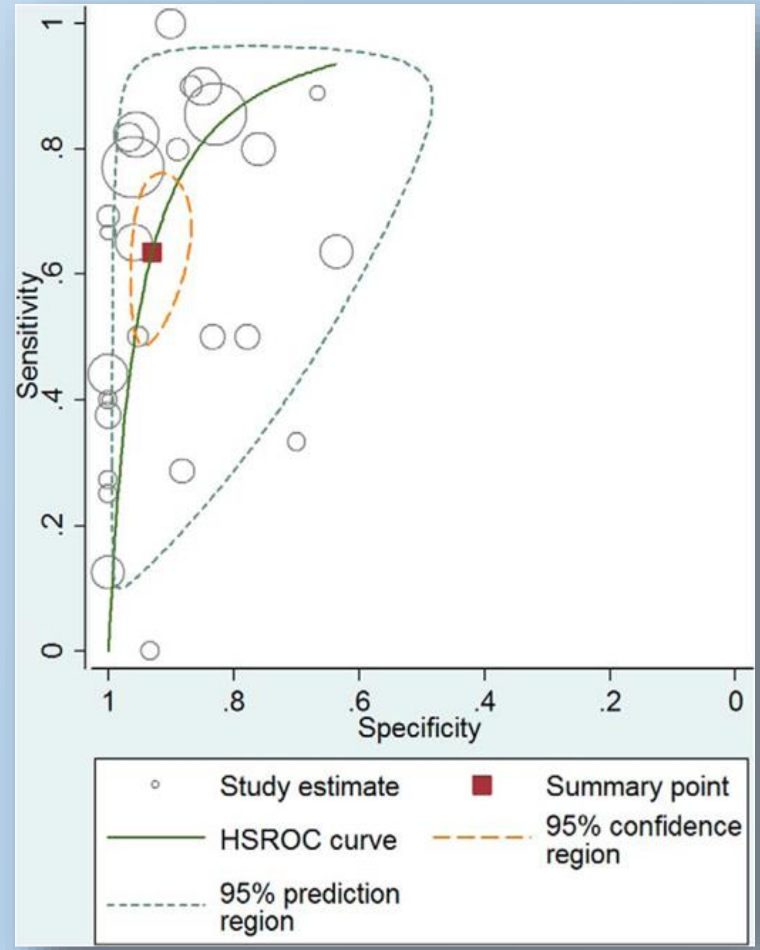


?????

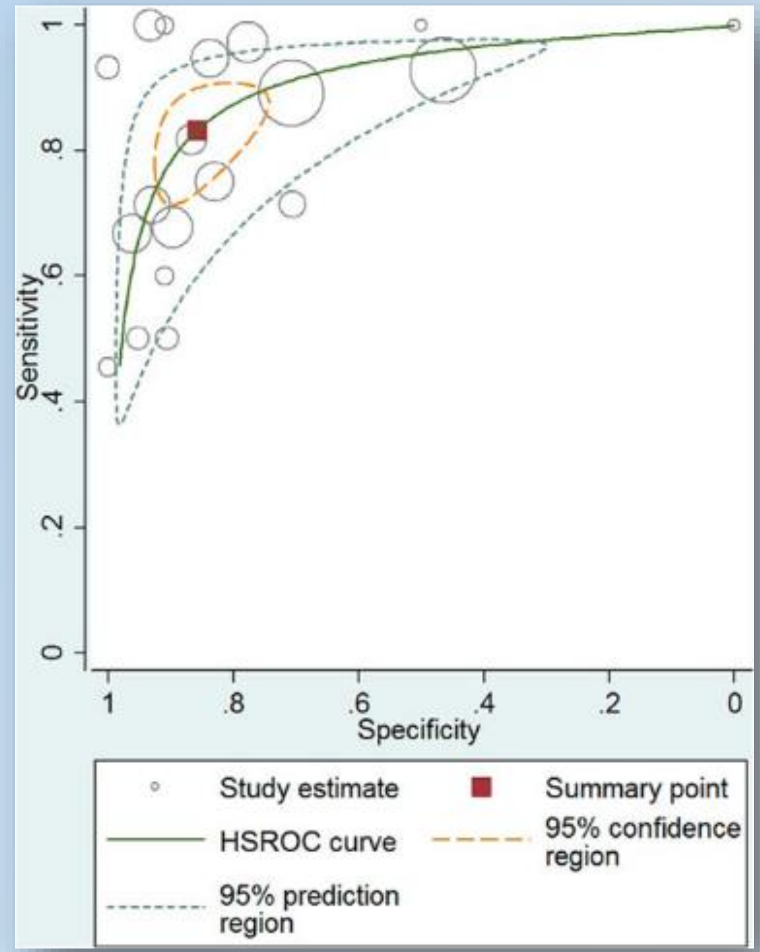
R Kazlauskaite, JCEM 2008

ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis

Both high- and low-dose ACTH stimulation tests <u>had similar diagnostic accuracy</u>



250 µg



1 µg

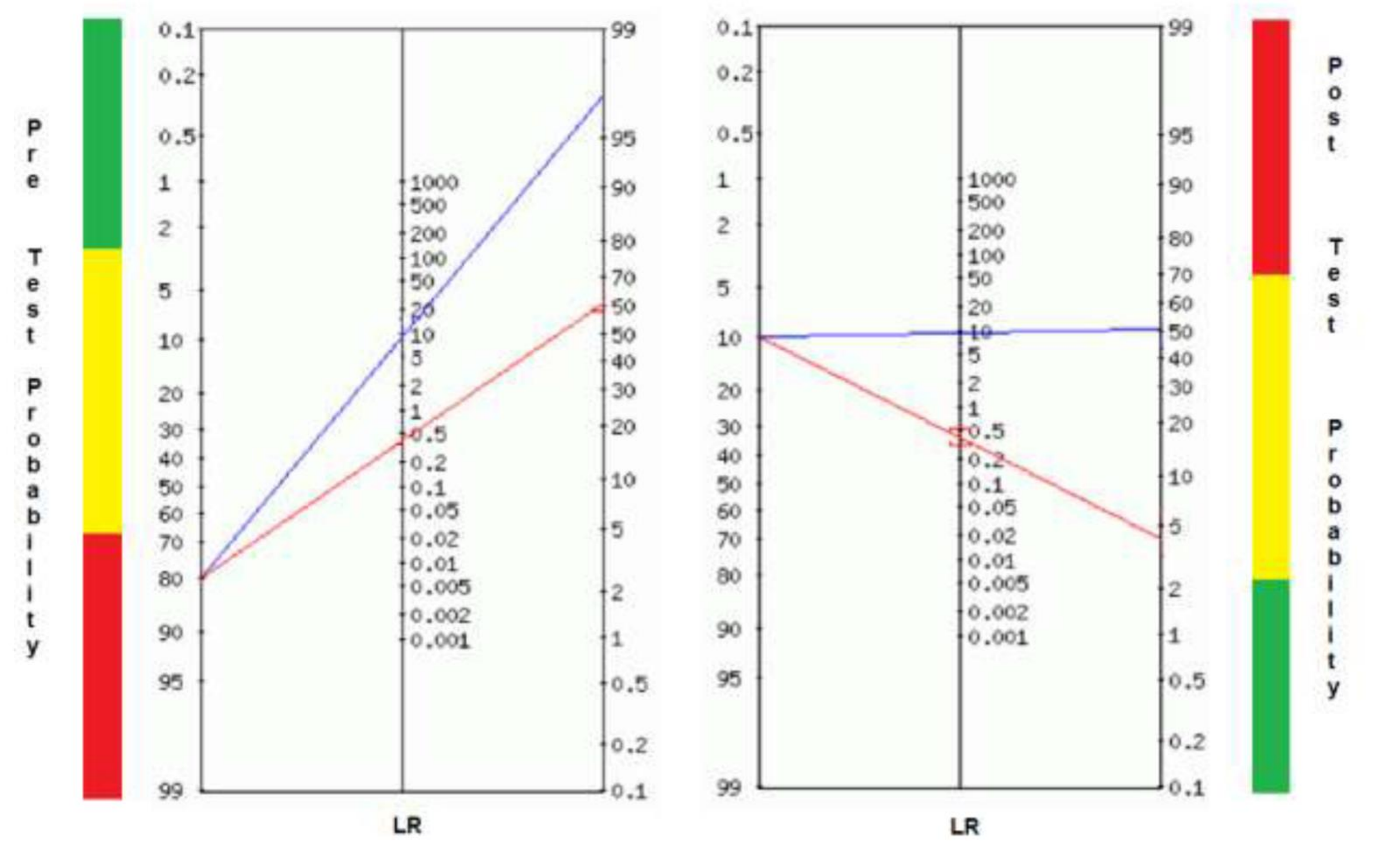
ITT or metyrapone test
AS GOLD STANDARDS

30 studies
1209 adults + 228 children
36% SAI

RESULTS:

- High variability
- 36% of AI in the cohort
- low = high dose
- Both tests are adequate to rule in, but not rule out, SAI

Ospina, J Clin Endocrinol Metab, 2016



High risk of CAI

Low risk of CAI

Blue line – positive high ACTH stimulation test. Red line – negative ACTH stimulation test.

“Understanding the pretest probability of disease and is essential to properly diagnosing AI” (Fleseriu JCEM 2016)

Ospina, J Clin Endocrinol Metab, 2016

conclusions

- ✓ Basal serum cortisol sufficient if ↓↓↓ or ↑↑↑
- ✓ ACTH test ….. Dose?
- ✓ LOW SENSITIVITY!!!!!
- ✓ Careful clinical approach

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Any question?