



Roma, 7-10 novembre 2019

**DOMENICA 10 NOVEMBRE 2019**



ITALIAN CHAPTER



**Misura degli steroidi nei liquidi biologici:  
appropriatezza, limiti e insidie diagnostiche**

**Criticità clinico - diagnostiche**

**Roberto Castello  
Medicina Generale  
AOUI Verona**



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# Conflitti di interesse



ITALIAN CHAPTER



Ai sensi dell'art. 4.5 su “Docenti e moderatori dell'evento”, pag. 8 del Manuale Nazionale di Accreditemento per l'erogazione di eventi ECM del 06/12/2018, dichiaro che negli ultimi 2 anni **non** ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.



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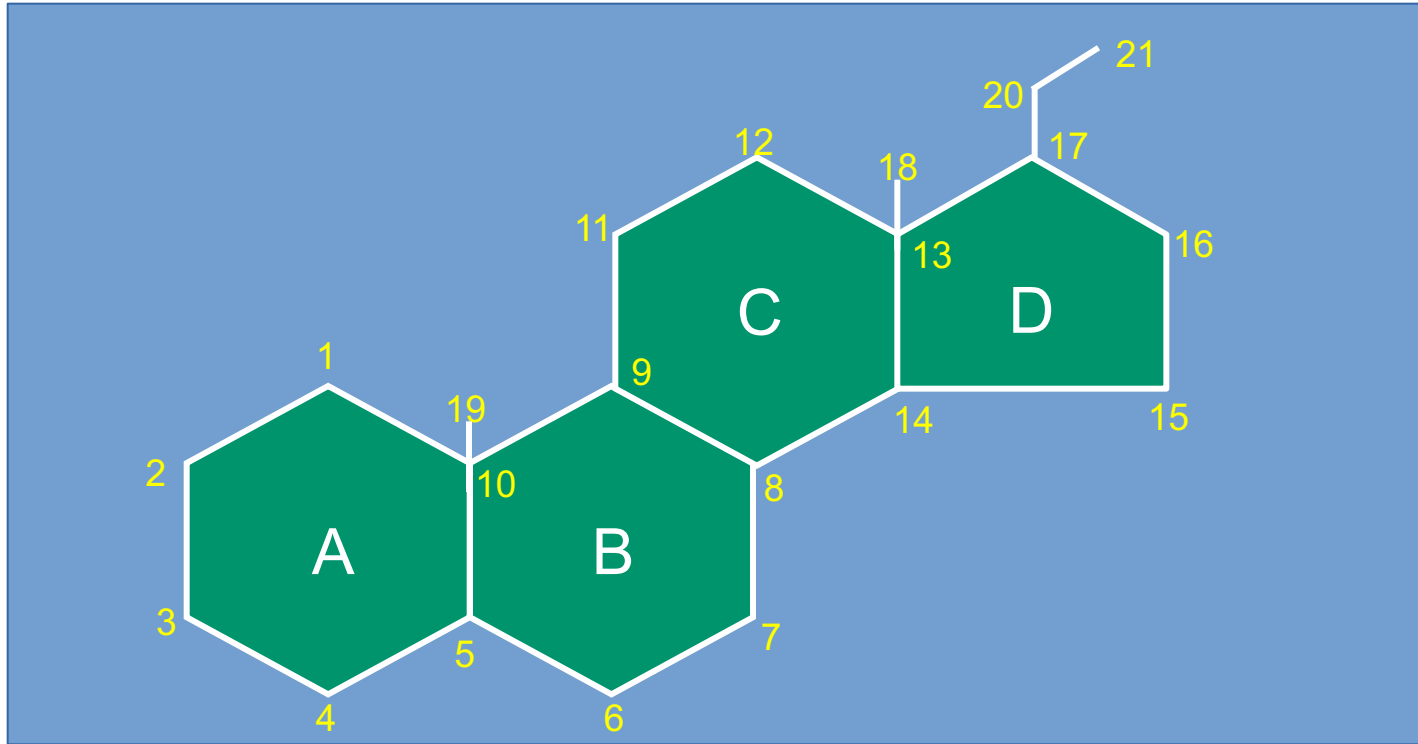


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# Struttura base degli steroidi



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**Ciclopentano peridro fenantrene**

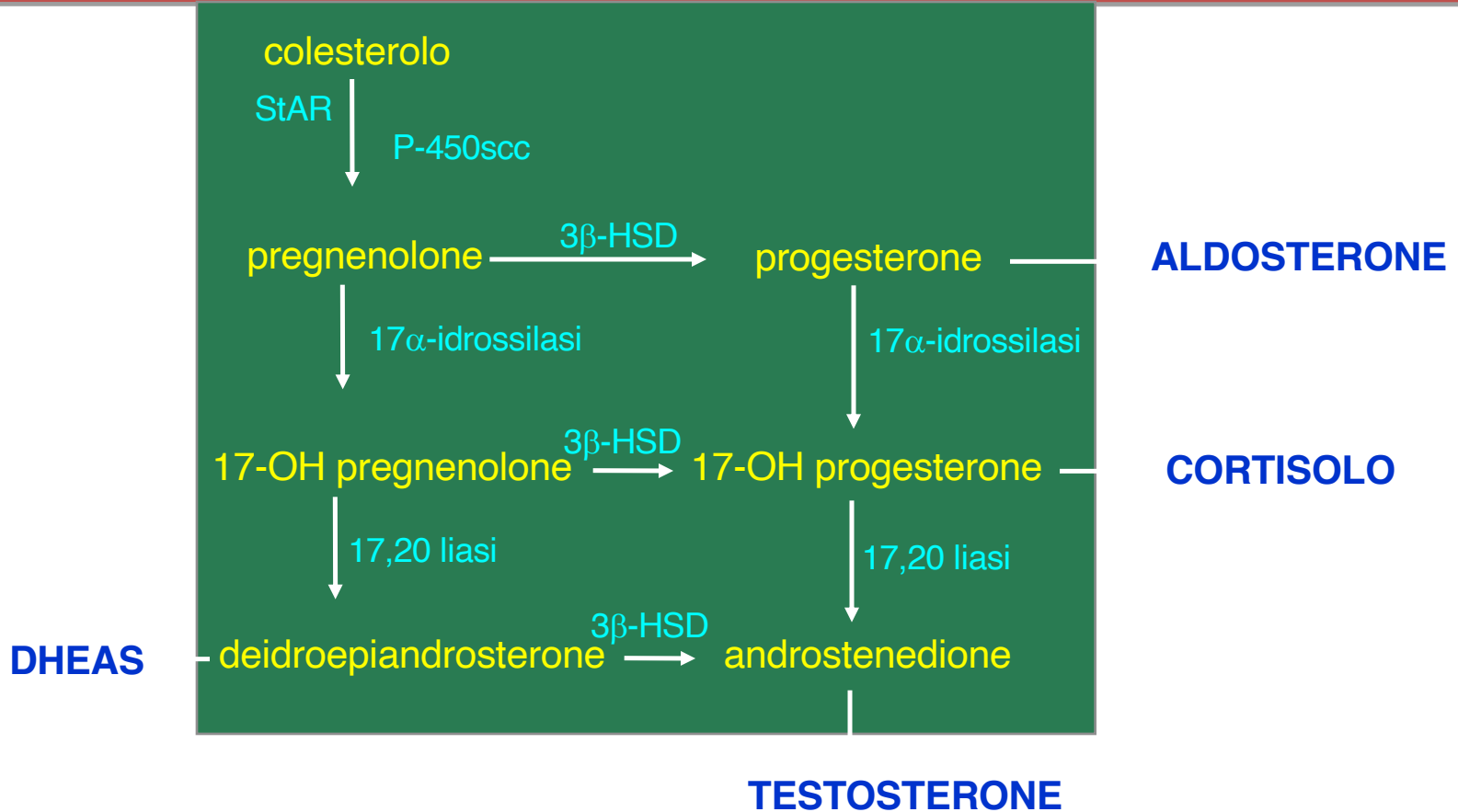


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# PRINCIPALI VIE BIOSINTETICHE DELLA STEROIDOGENESI



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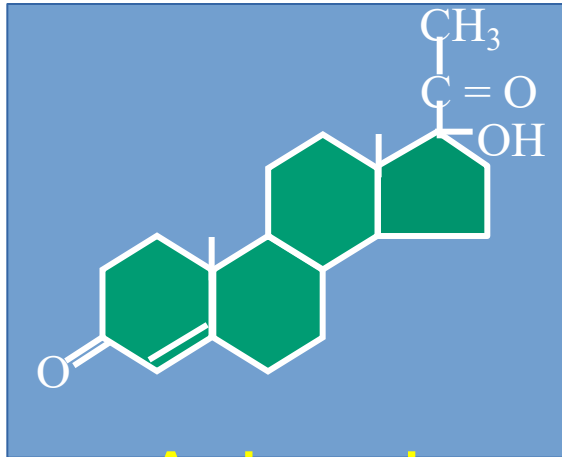
# Struttura dei principali steroidi



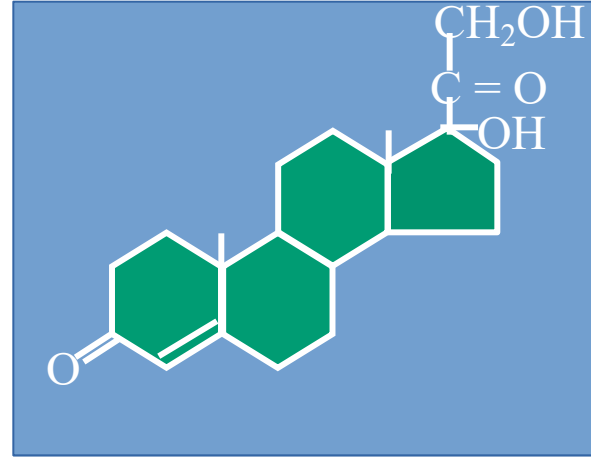
ITALIAN CHAPTER



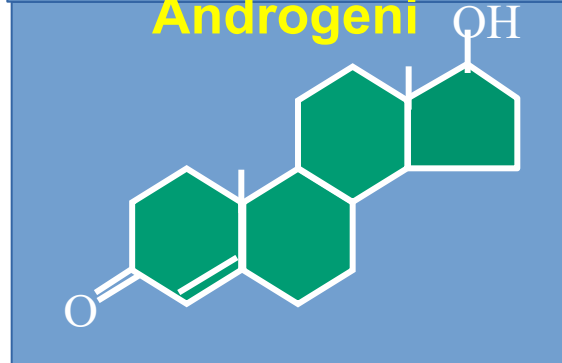
## Progesterone



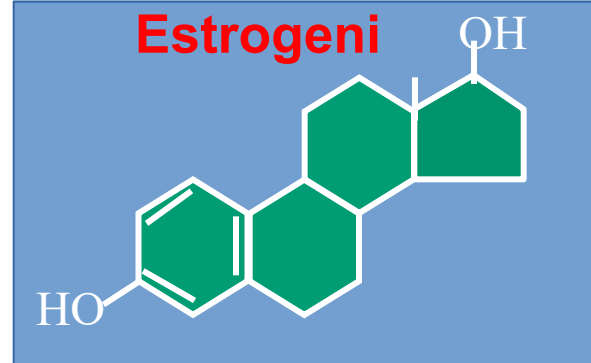
## Glucocorticoidi



## Androgeni



## Estrogeni





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**TESTOSTERONE  
CORTISOLO**





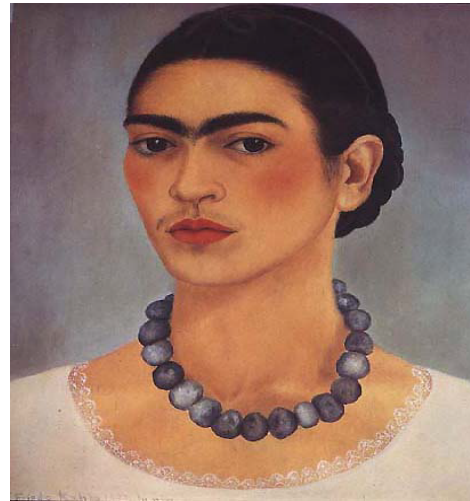
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# IPERANDROGENISMO



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**Sindrome clinicamente eterogenea determinata da un eccesso di androgeni circolanti o da una ipersensibilità tissutale agli androgeni**





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# PREVALENZA DELL'IPERANDROGENISMO IN ETÀ FERTILE



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## Da tutte le cause

~10%

- PCOS 5-7%
- Irsutismo idiopatico 2-3%
- Iperandrogenismo surrenalico funzionale 1-2%
- Deficit enzimatici ~ 0.1%
- Tumori assai rari



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# Manifestazioni cliniche



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**Irsutismo**



**Alopecia**



**Acne**



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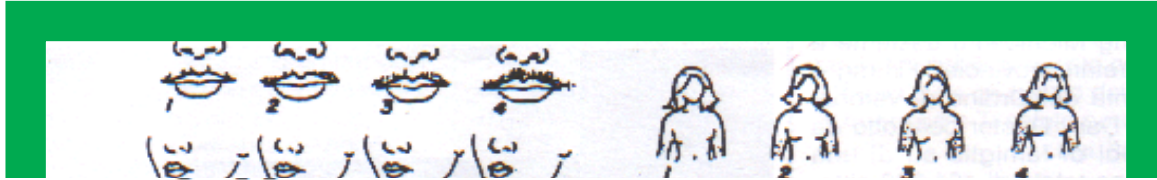


# SCHEMA PER LA VALUTAZIONE SEMI-QUANTITATIVA DELL'IRSUTISMO



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androgens. Considering only the remaining nine body areas, 4.3% of subjects studied had a score of greater than 7, leading these investigators to choose a score of 8 or more as defining hirsutism.



**Ferriman e Gallwey, modificato da Hatch et al, Am J Obstet Gynecol 1981**

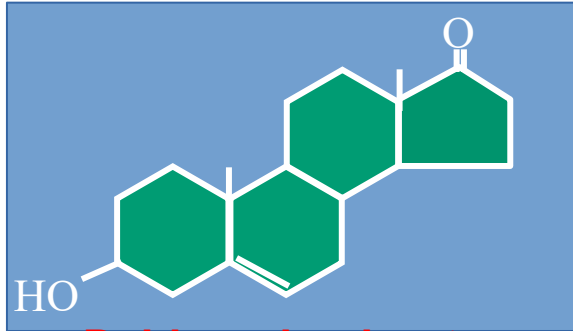


# Principali androgeni nella donna

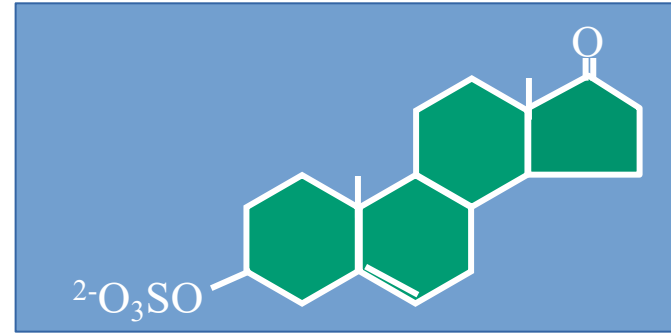


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**Deidroepiandrosterone**



**Deidroepiandrosterone solfato**



**Androstenedione**

**Testosterone**

**Diidrottestosterone**



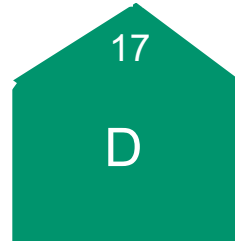
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## 17-cheto-steroidi



**DHEAS**

**DHEA**

**androstenedione**

**androsterone**

## 17-idrossi-steroidi



**testosterone**

**diidrotosterone**

**androstaniolo**

**androstenediolo**



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# Differential diagnosis in 873 patients evaluated for androgen excess: a *gynecological perspective*



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*Azziz, JCEM, 2003*

	Total n°	%
<b>Specific disorders:</b>		
- Androgen secretion neoplasms	2	<b>0.23</b>
- Congenital adrenal hyperplasia	6	<b>0.69</b>
- Non classic CAH	18	<b>2.06</b>
<b>Disorders of exclusion:</b>		
- PCOS	716	<b>82.02</b>
- Idiopathic hirsutism	39	<b>4.47</b>
- Hyperandrogenemia + hirsutism	59	<b>6.75</b>



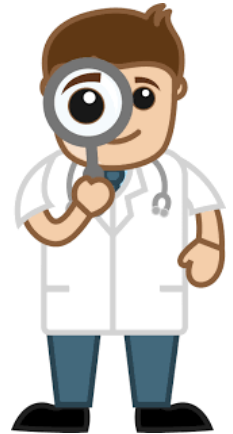
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# Quali esami chiedere per un inquadramento diagnostico in una donna irsuta con ciclo regolare?

- 1) 17OH-progesterone + testosterone totale
- 2) 1 + androstenedione e DHEA-S
- 3) 1 + testosterone libero
- 4) nessun esame





CLINICAL PRACTICE

## Hirsutism

Robert L. Rosenfield, M.D.

If hirsutism is mild (i.e., with a Ferriman–Gallwey score of 8 to 15) and menses are regular, with none of the features described above to suggest a secondary cause, it is reasonable to forgo laboratory evaluation, given the very high likelihood that the hirsutism is idiopathic. (Historically, hirsutism



SPECIAL FEATURE

Clinical Practice Guideline

### Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline

Kathryn A. Martin, R. Jeffrey Chang, David A. Ehrmann, Lourdes Ibanez, Rogerio A. Lobo, Robert L. Rosenfield, Jerry Shapiro, Victor M. Montori, and Brian A. Swiglo

#### 1.1 Diagnosis of hirsutism

1.1.1 We suggest against testing for elevated androgen levels in women with isolated mild hirsutism because the likelihood of identifying a medical disorder that would change management or outcome is low (2⊕○○○).



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life  
brain  
Eccellenza per  
la tua salute



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Esame	Risultato	U.M.	Valori di Riferimento
<b>ENDOCR.-ONCOL.</b>			
<b>FSH</b> Metodo: elettrochimiluminescenza Materiale: SIERO	3,5	mUI/ml	4,7 - 21,5 nella fase Ovulatoria 1,7 - 7,7 nella fase Luteinica 25,8 - 134,8 nella fase Menopausa 3,5 - 12,5 nella fase Follicolare
<b>17 Beta Estradiolo</b> Metodo: elettrochimiluminescenza Materiale: SIERO	18,2	pg/ml	12,4 - 233,0 nella fase Follicolare 41,0 - 398,0 nella fase Ovulatoria 22,3 - 341,0 nella fase Luteinica 5,0 - 138,0 nella fase Postmenopausa
<b>LH</b> Metodo: elettrochimiluminescenza Materiale: SIERO	4,2	mUI/ml	2,4 - 12,6 nella fase Follicolare 7,7 - 58,5 nella fase Postmenopausa 1,0 - 11,4 nella fase Luteinica 14,0 - 95,6 nella fase Ovulatoria
<b>Testosterone</b> Metodo: elettrochimiluminescenza Materiale: SIERO	0,30	ng/ml	0,08 - 0,48
<b>Deidroepiandrosterone Solfato (DHEA-S)</b> Metodo: chemiluminescenza Materiale: SIERO	2,56	ug/mL	0,35 - 4,30
<b>Androstenedione Delta 4 (R)</b> Metodo: chemiluminescenza Materiale: SIERO	2,38	ng/mL	0,30 - 3,30



# Iperandrogenismo biochimico

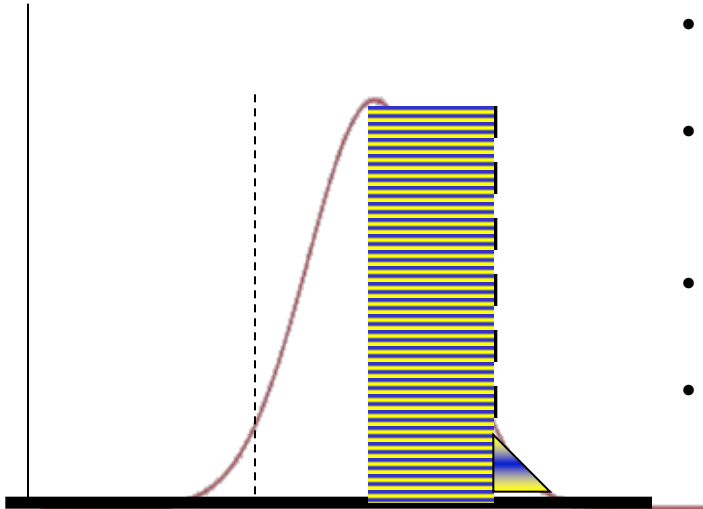


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**Molti laboratori definiscono i propri IR come valori normali al 95%:**

- **il 2.5% della popolazione normale risulterà al di sopra di tali limiti;**
- **se si dosano tutti e 4 gli androgeni, il 10% di tutti i normali potrebbe avere un risultato alterato;**
- **percentuale da incrementare ulteriormente se si inseriscono variabili calcolate;**
- **e se le pazienti sono esaminate in più occasioni, la probabilità di falsi positivi aumenta di un multiplo del numero di investigazioni.**





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AN CHAPTER

# VIRILISMO



**MICROMASTIA**



**IPERTROFIA  
CLITORIDEA**



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# Neoplasie androgeno-secernenti



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- **Insorgenza improvvisa**
- **Grado di irsutismo elevato**
- **Rapida evoluzione dell'irsutismo**

**Testosterone > 2 ng/ml**

**DHEAS < 3 µg/ml**

**Testosterone > 2 ng/ml**

**DHEAS > 6 µg/ml**



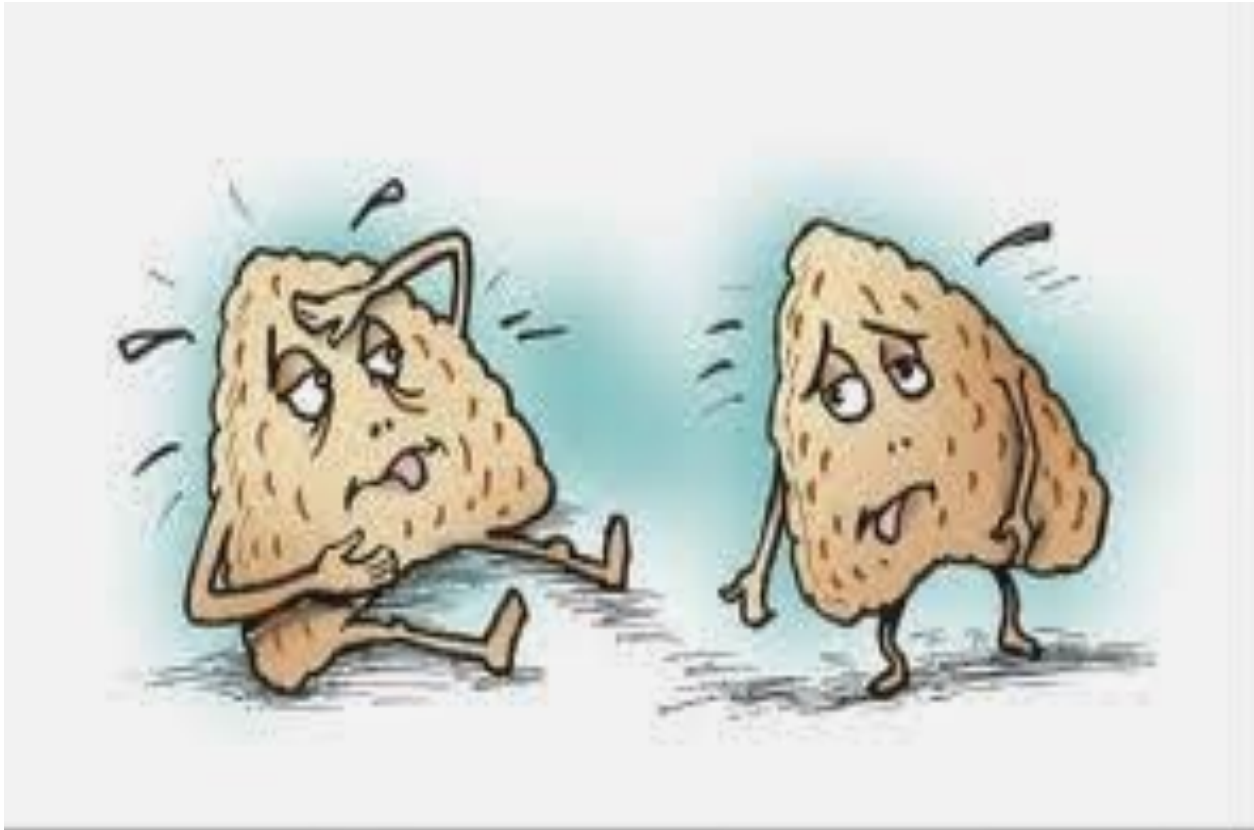
WIGHT



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# ... QUALE TESTOSTERONE DOSARE



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## È necessario dosare anche il testosterone libero?



0021-972X/07/\$15.00/0  
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(2):405-413  
Copyright © 2007 by The Endocrine Society  
doi: 10.1210/je.2006-1864

**POSITION STATEMENT: Utility, Limitations, and Pitfalls in Measuring Testosterone: An Endocrine Society Position Statement**

William Rosner, Richard J. Auchus, Ricardo Azziz, Patrick M. Sluss, and Hershel Raff



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# Iperandrogenismo biochimico



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## C'è mancanza di chiarezza su:

1. quale androgeno misurare
2. con che frequenza
3. quali sono i valori normali
4. che tecnica analitica sia preferibile impiegare



Clinical Chemistry 49, No. 8, 2003

Editorial



ALIAN CHAPTER

Roma, 7-10 novembre

*Immunoassays for Testosterone in Women: Better than a Guess?*

**... straordinariamente inaccurato<sup>1</sup>**

0021-972X/01/\$03.00/0  
The Journal of Clinical Endocrinology & Metabolism  
Copyright © 2001 by The Endocrine Society

Vol. 86, No. 6  
Printed in U.S.A.

## LETTER TO THE EDITOR

**An Extraordinarily Inaccurate Assay for Free  
Testosterone Is Still with Us**

William Rosner  
Department of Endocrinology  
St. Luke's-Roosevelt Hospital Center  
New York, New York 10019



Roma, 7-10 novembre 2019



ITALIAN CHAPTER



# JALM, 2016:194- 201

## ARTICLES

### Inaccurate First-Generation Testosterone Assays Are Influenced by Sex Hormone-Binding Globulin Concentrations

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Annemieke C. Heijboer,<sup>1\*</sup> Edo Savelkoul,<sup>1</sup> Adrian Kruit,<sup>2</sup> Erik Endert,<sup>3</sup> and  
Marinus A. Blankenstein<sup>1</sup>

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Trends & Insights for the Endocrine Community

# Endocrine news™

A Publication of The Endocrine Society

February 2007

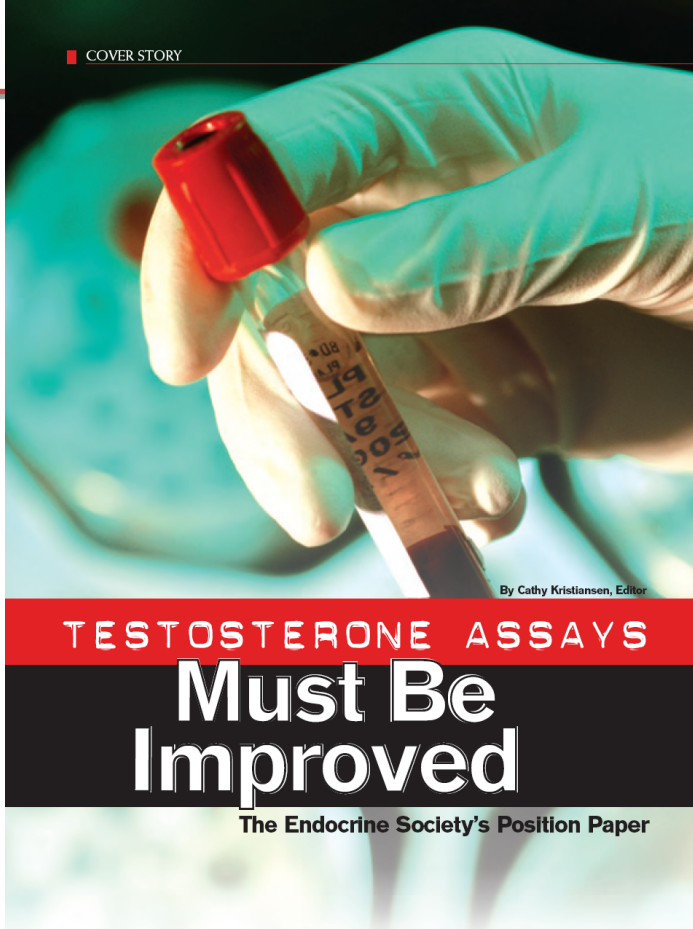
## Better Testosterone Assays Needed

The Endocrine Society's Position

Solving Fat's Mysteries

New Child Bone Markers

Congress Acts on Funding Bills



COVER STORY



LIAN CHAPTER

By Cathy Kristiansen, Editor

TESTOSTERONE ASSAYS

# Must Be Improved

The Endocrine Society's Position Paper



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# Situazione attuale ...



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# Additional effort is needed to improve accuracy/precision of measurements, especially at low concentrations



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Accepted Manuscript

Impact of testosterone assay standardization efforts assessed via accuracy-based proficiency testing

Cao Zhimin, Julianne Cook Botelho, Robert Rej, Hubert Vesper, J. Rex Astles

PII: S0009-9120(19)30088-8

DOI: <https://doi.org/10.1016/j.clinbiochem.2019.03.014>



**La standardizzazione degli steroidi che ha iniziato a fare CDC (HoSt Program) comincia a dare dei frutti: il bias inter-laboratorio nel 2007 per il testo totale era 16.5% e nel 2017 è del 2.8%, quindi ...**



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# TESTOSTERONE TOTALE

# TESTOSTERONE SALIVARE ?

**SAPERE DI NON SAPERE, QUALCHE VOLTA,  
È L' INIZIO DELLA SAGGEZZA**



# SINDROME DI CUSHING



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# SINDROME DI CUSHING



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SPECIAL FEATURE

Clinical Practice Guideline

## 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

### *Initial testing*

3.4 For the initial testing for Cushing's syndrome, we recommend one of the following tests based on its suitability for a given patient (Fig. 1) (1⊕○○○):

- 3.4.1 Urine free cortisol (UFC; at least two measurements)
- 3.4.2 Late-night salivary cortisol (two measurements)
- 3.4.3 1-mg overnight dexamethasone suppression test (DST)
- 3.4.4 Longer low-dose DST (2 mg/d for 48 h)

3.5 We recommend against the use of the following to test for Cushing's syndrome (1⊕○○○):

- Random serum cortisol or plasma ACTH levels

CORTISOLEMIA

CORTISOLURIA

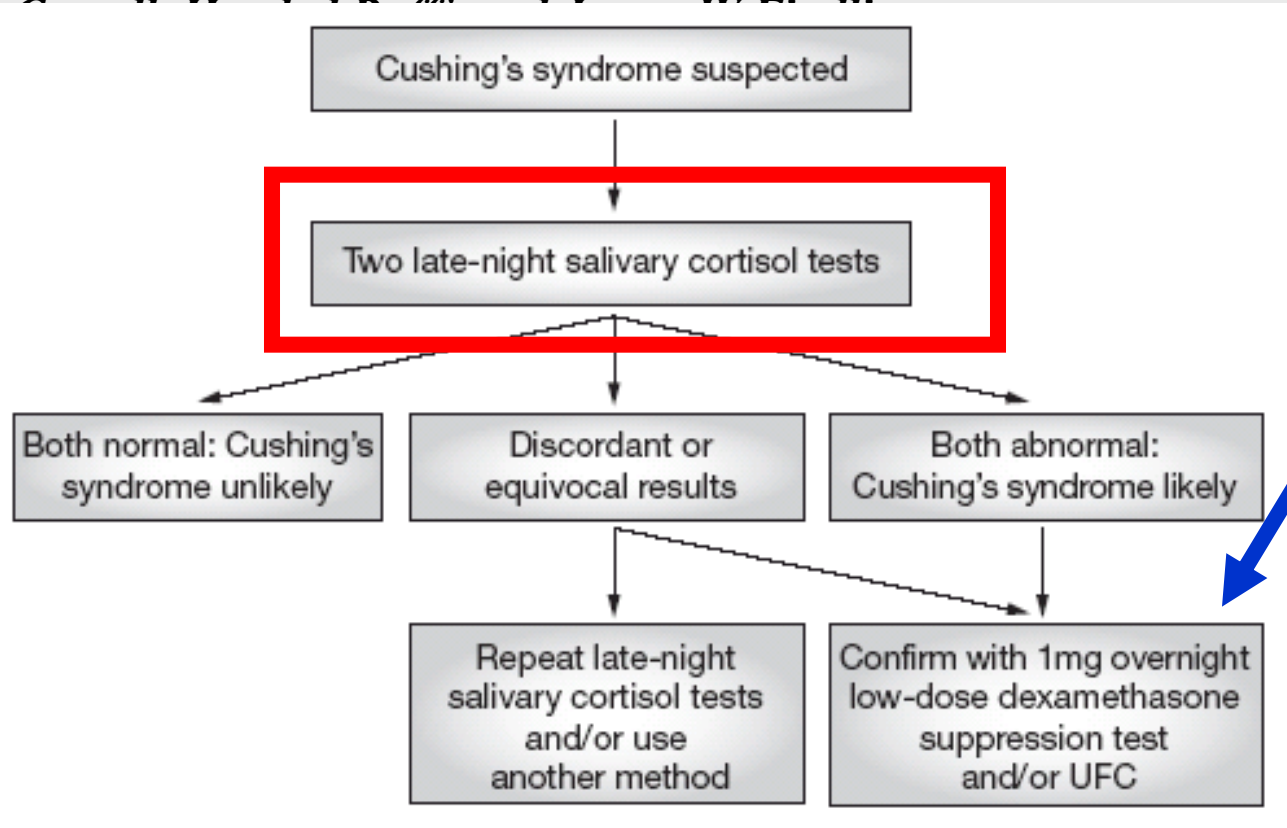
TEST DI NUGENT

CORTISOLO SALIVARE





# Late-night salivary cortisol measurement in the diagnosis of Cushing's syndrome





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**TESTOSTERONE TOTALE**





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# Quesiti



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- **A chi?**
- **Quando?**
- **Perche è importante?**
- **Tutti i metodi sono uguali?**
- **Quali sono gli intervalli di riferimento?**
- **C'è "un limite inferiore di normalità"?**





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# Raccomandazioni nell'utilizzo e nell'interpretazione dei dosaggi del testosterone nei bambini



ITALIAN CHAPTER



- ✓ Determinazione del *testosterone totale* in casi di pubertà precoce o ritardata

Intervalli di riferimento stabiliti in funzione di età e stadio puberale



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# Valori di testosterone nel maschio in relazione allo stadio di Tanner



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<b>STADIO 1</b>	<b>&lt; 30 ng/dl</b>
<b>STADIO 2</b>	<b>30- 95 ng/dl</b>
<b>STADIO 3</b>	<b>70 – 210 ng/dl</b>
<b>STADIO 4</b>	<b>180 - 550 ng/dl</b>
<b>STADIO 5</b>	<b>&gt; 400 ng/dl</b>

CORTESIA DOTT GAROFALO



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# LATE ONSET HYPOGONADISM



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**“A clinical and biochemical syndrome associated with **advancing age** and characterized by typical symptoms and a **deficiency in serum testosterone levels.**”**

ANDROLOGY 2005



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# Endocrine Aspects of Male Sexual Dysfunctions

J Sex Med 2010;7:1627–1656



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Jacques Buvat, MD,\* Mario Maggi, MD,<sup>†</sup> Louis Gooren, MD,<sup>‡</sup> Andre T. Guay, MD,<sup>§</sup> Joel Kaufman, MD,<sup>¶</sup>  
Abraham Morgentaler, MD,\*\* Claude Schulman, MD,<sup>††</sup> Hui Meng Tan, MD,<sup>‡‡</sup> Luiz Otavio Torres, MD,<sup>§§</sup>  
Aksam Yassin, MD,<sup>¶¶</sup> and Michael Zitzmann, MD\*\*\*

Journal of Andrology, Vol. 30, No. 1, January/February 2009  
Copyright © American Society of Andrology

## Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations

C. WANG\*, E. NIESCHLAG,<sup>†</sup> R. SWERDLOFF\*,

- Serum sample for total testosterone (TT) determination.



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# Cosa dovrebbe sapere il clinico



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- **Metodo usato dal laboratorio**
- **Costruzione degli intervalli di riferimento utilizzati**
- **Unità di misura e fattori di conversione**



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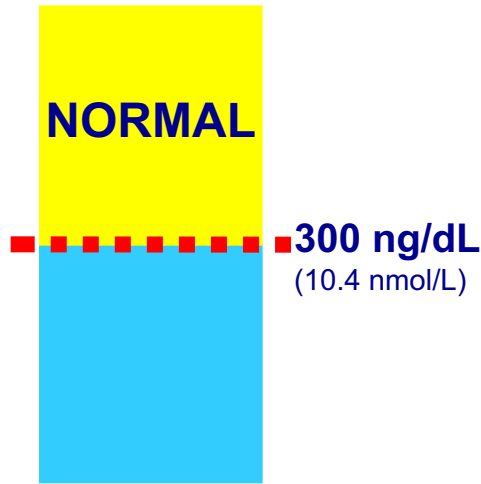
# THRESHOLDS FOR THE DIAGNOSIS OF HYPOGONADISM



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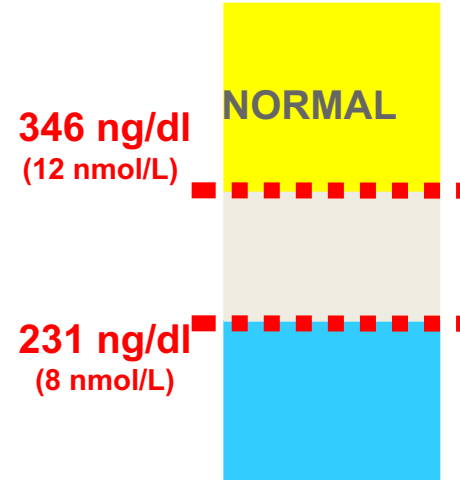


## No Universal T Threshold available



**Endocrine Society**

Bhasin S *et al. JCE&M*  
95:2536-59, 2010



**ISA, ISSAM and EAU**

Wang C *et al. J Androl* 30:1-9, 2009

Buvat J *et al. J Sex*  
*Med*;10:245-84, 2013



Roma, 7-10 novembre 2010



IN CHAPTER

T (ng/ml)

T (nM)

5.0

17

No terapia con testosterone

3.5

12

3.0

10.4

2.31

8

0.5

2

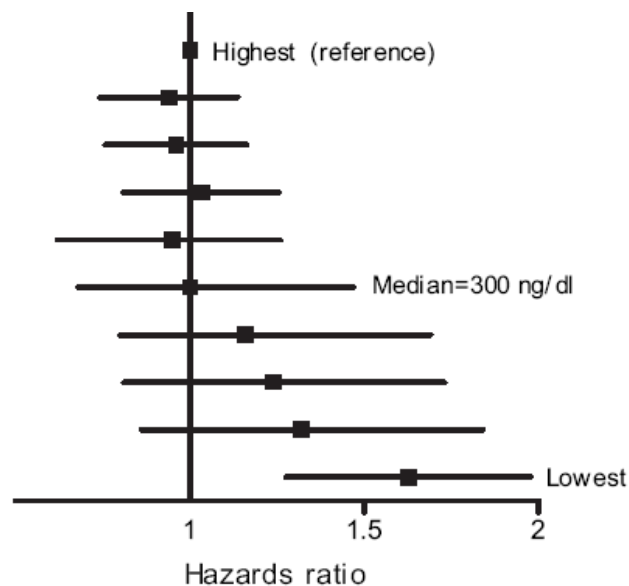
Terapia con testosterone



## Low Serum Testosterone and Mortality in Older Men

Gail A. Laughlin, Elizabeth Barrett-Connor, and Jaclyn Bergstrom

Department of Family and Preventive Medicine, School of Medicine, University of California, San Diego, La Jolla, California 92093



**FIG. 1.** All-cause mortality according to deciles of total testosterone adjusting for age, BMI, waist to hip ratio, current smoking, alcohol use, and exercise. The *squares* represent point estimates for HRs, the *lines* indicate 95% CIs. The median total testosterone values for deciles 1–10 were 171, 209, 241, 266, 288, 314, 338, 370, 422, and 507 ng/dl, respectively.

# Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality

Sharma R et al. Eur Heart J.2015;21:36(40):2706-2715

**83010** soggetti con diagnosi di ipo-testosteronemia (1999 – 2014)

**Età > 50 aa** (mediana 66 aa per ogni gruppo)

**Follow-up 4.6 – 6.2 anni**

**43931**

**T-th si;**

**T normale**

**25701**

**T-th si;**

**T NON normale**

**13378**

**T-th no**

**T-th con T normale vs non T-th** durante follow-up

**in T-th**

**56% minore probabilità di decesso**

**24% minore probabilità di infarto miocardico**

**36% minore probabilità di ictus**





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## Testosterone Therapy in Men With Hypogonadism: An Endocrine Society\* Clinical Practice Guideline



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J Clin Endocrinol Metab, May 2018, 103(5):1–30



The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of randomized, placebo-controlled trials.

It is important to measure T concentrations in the patient group once a steady-state has been achieved. Multiple dose titrations are usually necessary to maintain T concentrations in the therapeutic range in hypogonadal men who are receiving T therapy.

**The principal goal: to restore the serum testosterone concentration to the normal range**



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# Endogenous steroids and financial risk taking on a London trading floor

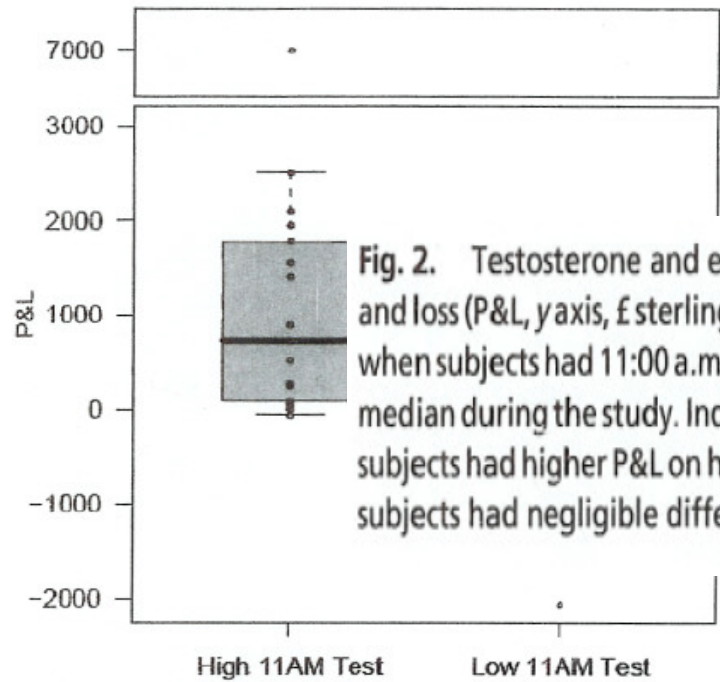


IAN CHAPTER



J. M. Coates\*<sup>1†</sup> and J. Herbert\*\*<sup>5</sup>

PNAS | April 22, 2008 | vol. 105 | no. 16



**Fig. 2.** Testosterone and economic return. Boxplot showing average profit and loss (P&L, y axis, £ sterling) made between 11:00 a.m. and 4:00 p.m. on days when subjects had 11:00 a.m. testosterone above (High) and below (Low) their median during the study. Individual data points are shown. Fourteen out of 17 subjects had higher P&L on high testosterone days than on low; the remaining subjects had negligible differences.



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ITALIAN CHAPTER

**GRAZIE PER L'ATTENZIONE**