



# Harmonisatie van Hormoonbepalingen: voor wie eigenlijk?

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VU medisch centrum



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## Harmonie (van Dale 14<sup>e</sup> uitgave; 2005)



- Samenwerking of verband van een aantal zaken tot en welgeordend en aangenaam aandoend geheel; het aangepast zijn van elementen aan elkaar en aan hun milieu *syn*: overeenstemming
- Goede verstandhouding; *syn*: eensgezindheid
- Aangenaam klinkende vereniging van gelijktijdige of elkaar opvolgende tonen
- Overeenstemming van al de stemmen, partijen van een muziekstuk
- De gezamenlijke blaas- en slaginstrumenten in een orkest en de bespelers ervan
- Vereniging van personen die harmoniemuziek maken



## Harmoniseren

Van Dale 14<sup>e</sup> uitgave; 2005

- Harmonisch, tot een goed samenklinkend of samengaand geheel maken
- Goed met elkaar overweg kunnen, bij elkaar passen



## Wie heeft baat bij Harmonisatie van uitslagen van hormoon bepalingen?

- Patiënt
- Aanvrager: Huisarts / specialist
- Laboratorium
- Ziekenhuis
- Zorgverzekeraar
- ?
- ?



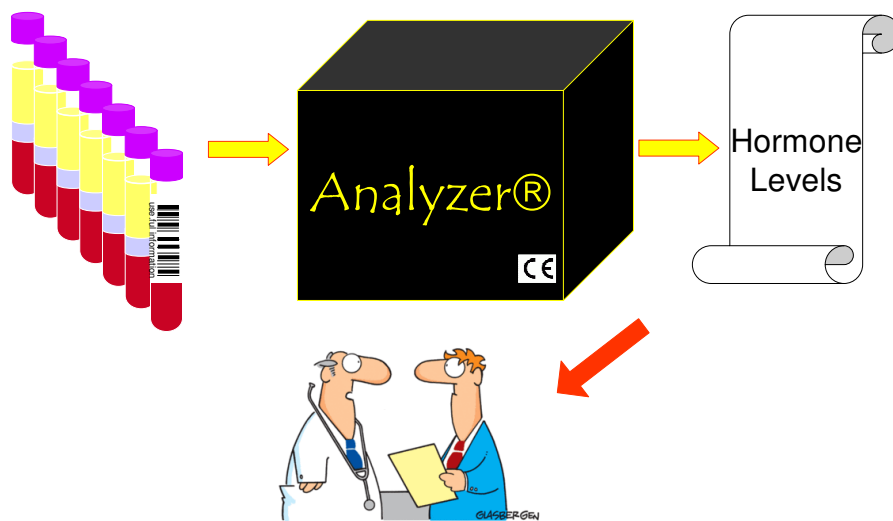
## PubMed Search (June 2011)

Search term	No of cites
Laboratory results	768419
Immunoassay	389208
Harmonization	1911
<b>Harmonization Laboratory results</b>	<b>223</b>
<b>Immunoassay Harmonization</b>	<b>51</b>
Hormone Assays	20407
<b>Hormone Assay Harmonization</b>	<b>14</b>

Conclusion from literature:

Harmonization often taken as **standardization**

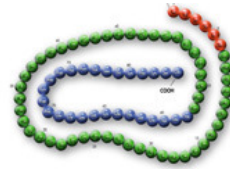
## Hormone Assays Anno 2011





## Awareness of Clinicians is insufficient

Examples: **Parathyroid Hormone (PTH)**  
and  
**Prostate specific Antigen (PsA)**

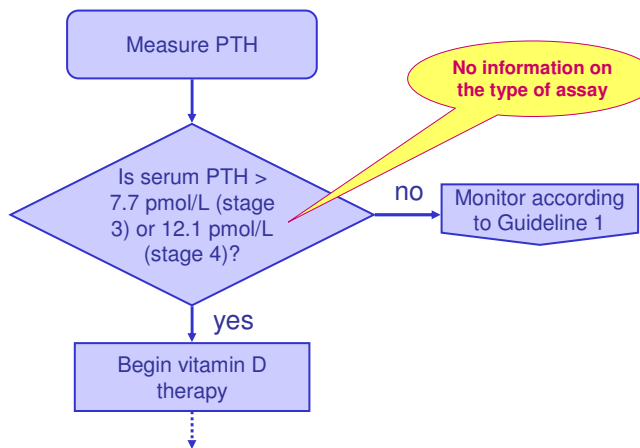


Parathyroid Hormone

## K/DOQI Clinical Guideline #8



In Chronic Kidney Disease patients, stages 3 and 4, with stable renal function, compliant with visits and medications with serum phosphorus levels < 1.49 mmol/L, Calcium < 2.37 mmol/L and 25(OH)VitD ≥ 75 nmol/L:



Am J Kidney Dis 42:S1-S202, 2003 (suppl 3)

## PTH Molecular Heterogeneity

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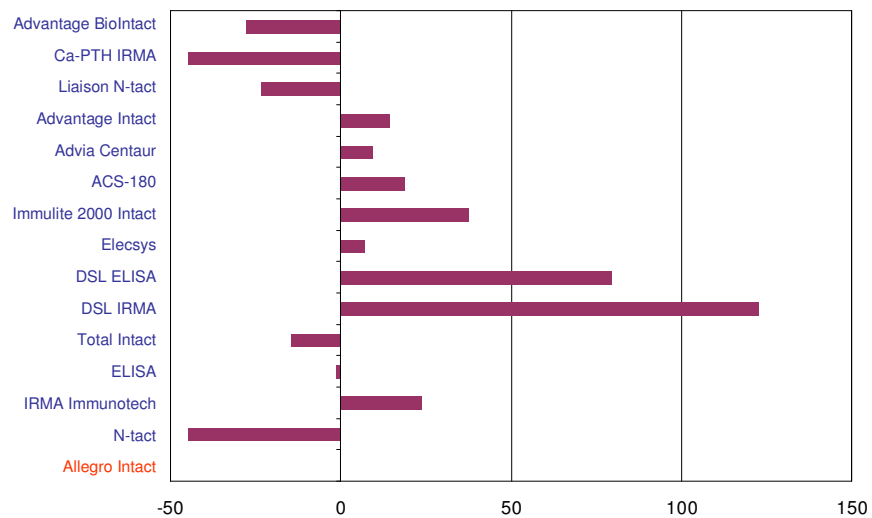
### Estimation of the percentage of total immunoreactivity

	Intact 1-84 PTH (%)	C-terminal Fragments (%)
Normal	20 14.0 intact 1-84 PTH 4.4 N-terminally truncated 1.6 amino-PTH	80
CRF	5 2.5 intact 1-84 PTH 1.8 N-terminally truncated 0.7 amino-PTH	95

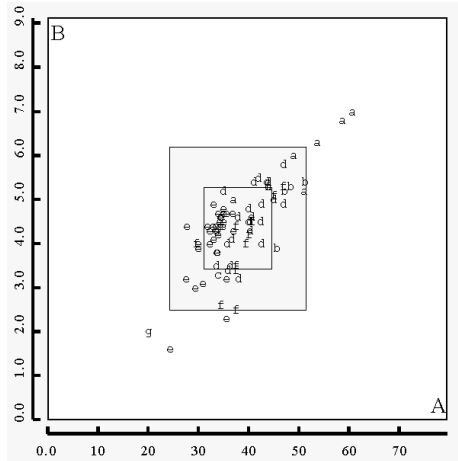
Torres PU; Kidney Int 2006;70:240-243

## Bias of commercial PTH assays\*

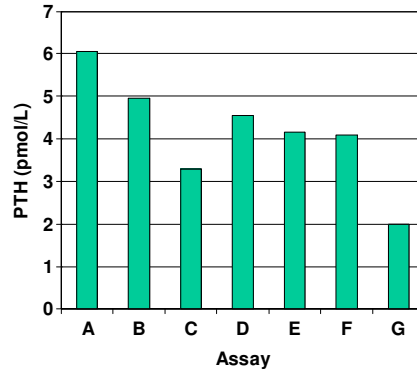
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\* Souberbielle; Kidney Int 2006;70:345-350



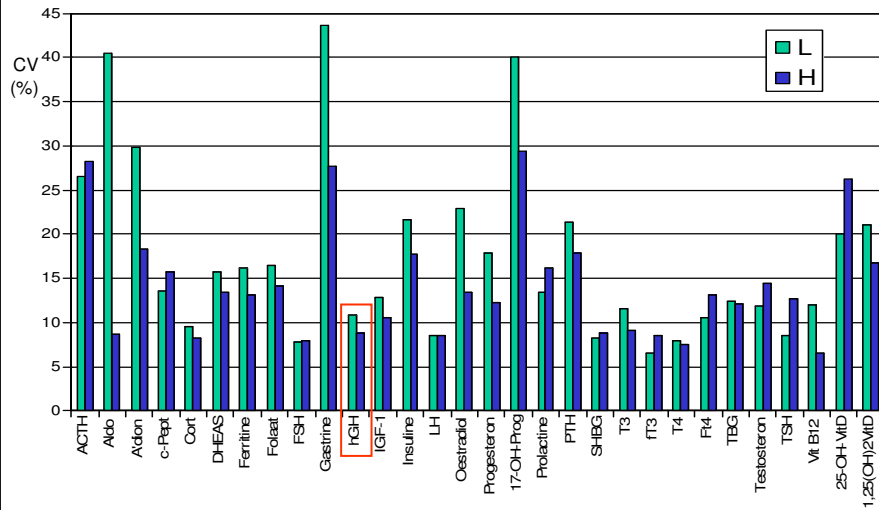
Mean Result per Assay



How serious is the problem?

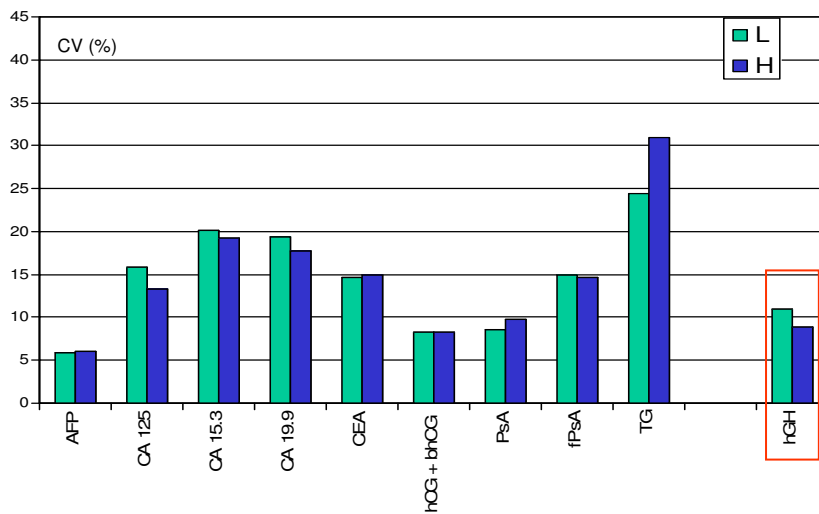
## Between Lab CV 2011-2 Endocrinology

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## Between Lab CV 2011-2 Tumour Markers

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Papers in Press. Published May 24, 2011 as doi:10.1373/clinchem.2010.151472  
The latest version is at <http://www.clinchem.org/cgi/doi/10.1373/clinchem.2010.151472>

Clinical Chemistry 57:7  
000-000 (2011)

Cancer Diagnostics

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### Between-Method Differences in Prostate-Specific Antigen Assays Affect Prostate Cancer Risk Prediction by Nomograms

Carsten Stephan,<sup>1,2,\*</sup> Kerstin Siemßen,<sup>1\*</sup> Henning Cammann,<sup>3</sup> Frank Friedersdorff,<sup>1</sup> Serdar Deger,<sup>1</sup> Mark Schrader,<sup>1</sup> Kurt Miller,<sup>1</sup> Michael Lein,<sup>1,2,4</sup> Klaus Jung,<sup>1,2</sup> and Hellmuth-A. Meyer<sup>1</sup>

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**“CONCLUSIONS:** The accuracy of the PCa probabilities predicted according to different nomograms is limited by the lack of agreement between the different PSA assays. This difference between methods may lead to unacceptable variation in PCa risk prediction. A more cautious application of nomograms is recommended”.



Papers in Press. Published May 24, 2011 as doi:10.1373/clinchem.2011.166041  
The latest version is at <http://www.clinchem.org/cgi/doi/10.1373/clinchem.2011.166041>

Clinical Chemistry 57:7  
000-000 (2011)

Editorials

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### Patient Safety and Clinical Effectiveness as Imperatives for Achieving Harmonization Inside and Outside the Clinical Laboratory

Ronald W. McLawhon<sup>1\*</sup>

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“...yet a striking majority of our physician and surgeon colleagues still fail to grasp or understand the limitations of current laboratory measurements, the lack of interchangeability of results obtained by different analytical methods, and the resulting effects on interpretation, clinical decision-making, and patient management” ...

“...we must remain vigilant in raising awareness that current laboratory results are neither standardized nor harmonized and may lead to erroneous decisions with serious consequences (i.e., just plugging the numbers into a risk-calculation nomogram can give misleading results)”.





“... Bij het ontbreken van een zekere intra-uteriene zwangerschap of EUG levert de serum-hCG-spiegel belangrijke aanvullende informatie op. Bij aanwezigheid van een ectopic mass en/of vrij vocht in de peritoneale holte is een **serum-hCG-spiegel > 1500 IU/l** (International Reference Preparation) vrijwel bewijzend voor een EUG....”

## Consequences:

Not much improvement since 2006...

Laboratories must protect clinicians against unawareness and report reliable results

Clinicians should consult clinical chemists when designing clinical guidelines containing decision rules based on laboratory results.



Clin Chem Lab Med 2011;49(1):43-48 © 2011 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2011.003

Opinion Paper

## Harmonization of free thyroid hormone tests: a mission impossible?

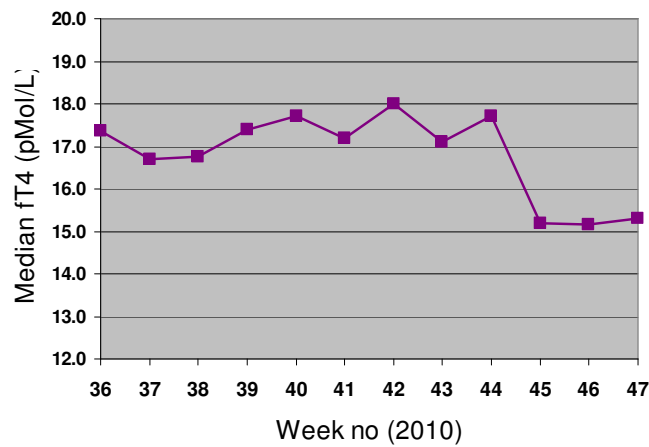
Giorgio Iervasi and Aldo Clerico\*

CNR Institute of Clinical Physiology, Scuola Superiore  
Sant'Anna, Pisa, Italy

## Could harmonization have prevented this?



Weekly Median Patient Results



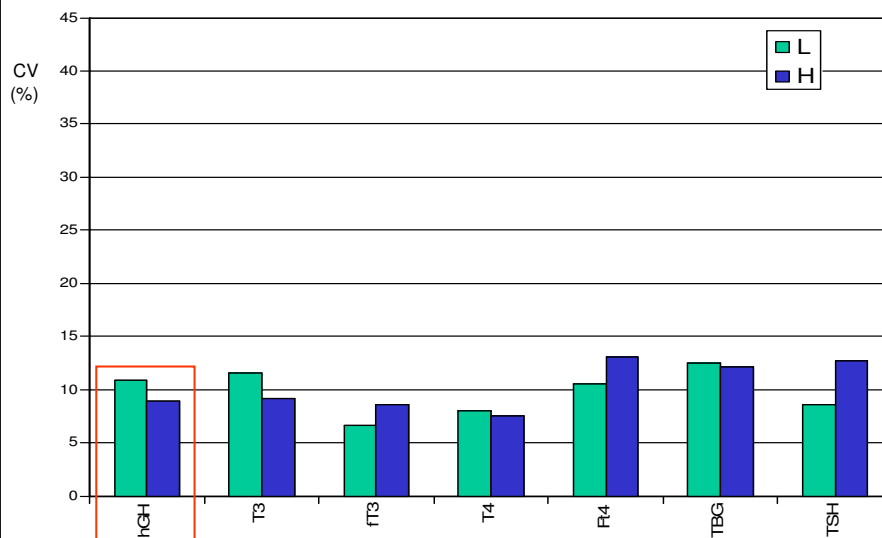


## Principal factors affecting Free Thyroid Hormone assays

- Temperature
- Serum dilution
- Non-esterified fatty acids
- Auto-antibodies
- Heterophilic antibodies
- Drugs interfering with serum protein binding of thyroid hormones (i.e., aspirin, heparin, furosemide) diphenylhydantoin, carbamazepine, phenytoin, non-steroidal anti-inflammatory drugs, NSAIDs, sulfonyleureas
- Change in affinity of binding protein (such as familial hyperthyroxinemia with dysalbuminemia)
- Change in concentration of protein binding (such as pregnancy, estrogen treatment, clofibrate, 5-fluorouracil, androgen treatment, glucocorticoids, hypoalbuminemia)

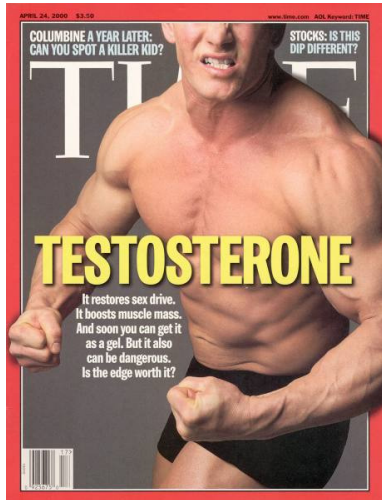
Iervasi and Clerico Clin Chem Lab Med 2011;49:43-48

## Between Lab CV 2011-2 Thyroid



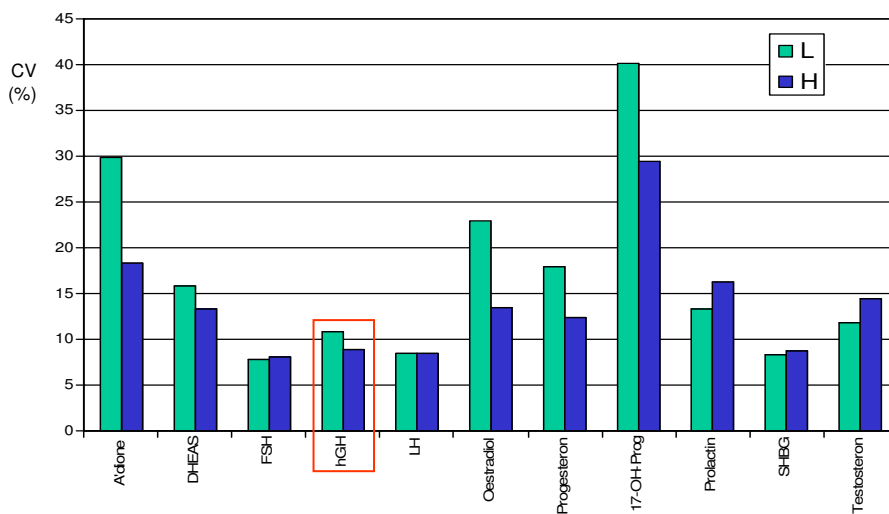
## What about Sex Steroids?

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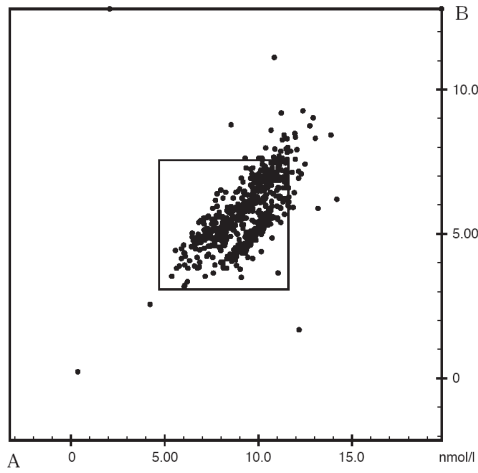
## Between Lab CV 2011-2 Fertility

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## International QC of Testosterone Assay\*

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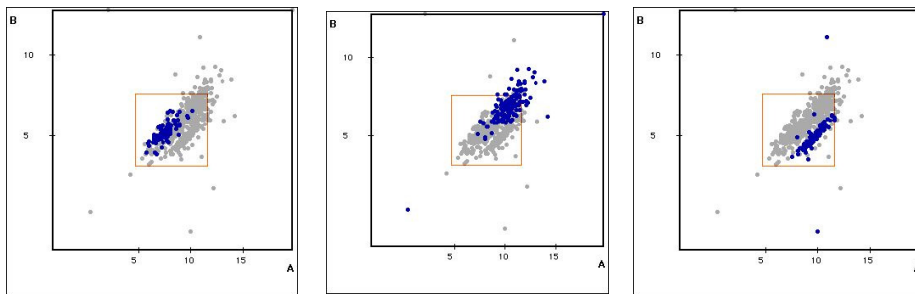


Sample	A	B
N	687	687
Mean	9.35	5.68
SD	1.48	1.15
CV (%)	15.9	20.3

\*Courtesy DGKL; HM 2007/4

## Three Luminescence T Assays

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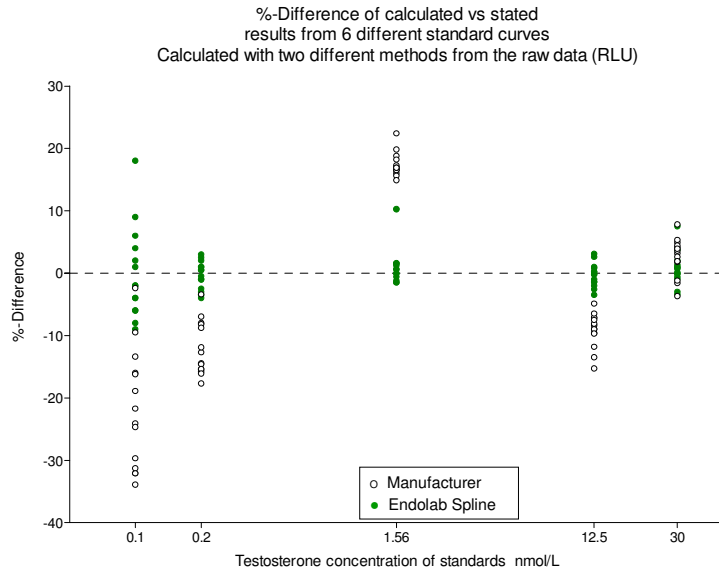


\*Courtesy DGKL; HM 2007/4



## Differences in Calculation

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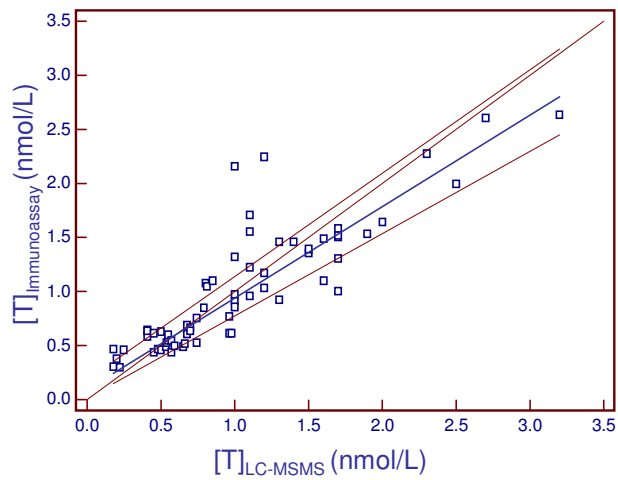


## Immunoassay vs LC-MSMS Testosterone

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Can this be "Harmonized"?



## Some Issues in Immunoassays

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- Sensitivity
- Dynamic range
- Specificity
  - Cross reactivity vs metabolites, drugs, medication etc
  - Molecular form of the analyte
- Accuracy
- Reproducibility
  - Within assay and reagent lot
  - A different concentrations
  - Between assays and reagent lots
- Interferences
- Mode of calculation

## Critical Factors in Immunoassays

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- The specimen
- The antibodies
- The standardization
- Other (proprietary) reagents
- Release of analyte from binding protein(s)
- Assay Design
- Separation Method
- Detection Method
- Calculation of Result
- Assay Platform
- Technician



## Interferences in Immunoassays

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- Cross reactivity
- Alternative binding proteins
- HAMA's
- Endogenous antibodies
- Drugs and drug metabolites (prednisone/prednisolone)
- Hemolysis; lipids; bilirubin
- Pre-analytical conditions, such as clotting activator
- .....

## Harmonization of Hormone Assays

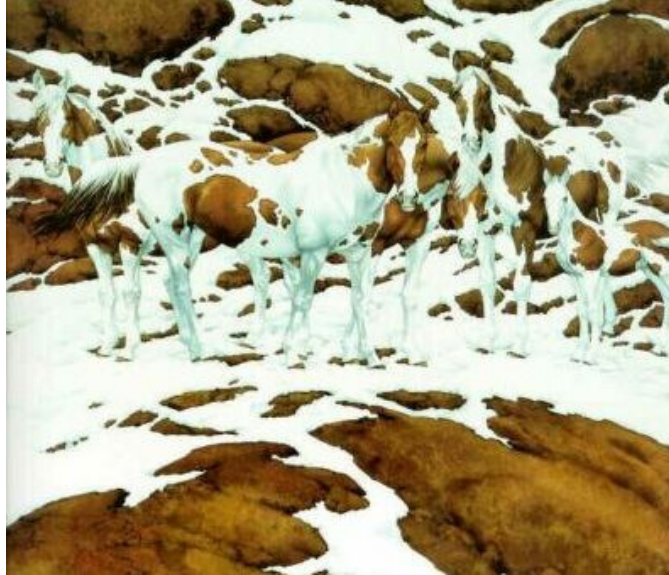
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- **For:** PATIENTS and DOCTORS, as they will benefit
- **By:** Primarily MANUFACTURERS as they claim to be “approved” or “certified” and their systems are virtually inaccessible to the user.
- **But:** LABORATORIES should be vigilant: after all, **we are responsible for the result**

## Harmony with Surrounding

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## In Harmonie met mezelf?

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(SKZL 1998)