UMC Utrecht

Target value: the holy grail or an avatar?

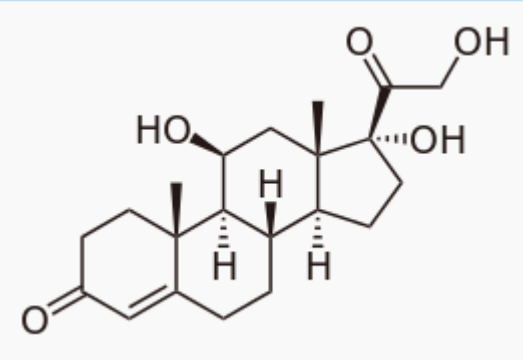
Sectie endocrinologie

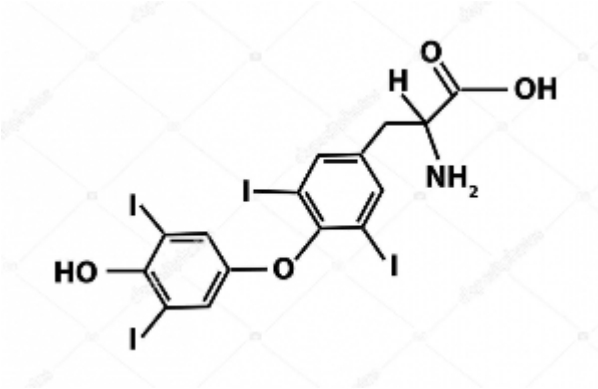
Eef Lentjes

1. Targetwaarden voor de “gemakkelijke” hormonen

- Eenduidige stoffen
- Commuteerbaar monster

- Steroiden
- Schildklierhormonen
- metanefrines





UMC Utrecht

Database of higher-order reference materials, measurement methods/procedures and services

JCTLM
Accurate results for patient care

JCTLM

Analyte	Matrix/Material	Name of the reference material	Producer	Quantity	Range of certified values in reference material	Range of expanded uncertainties for certified value
cortisol	cortisol crystalline material	SRM 921, cortisol	NIST (National Institute of Standards and Technology), United States Phone : +1 301 975 6776 Fax : +1 301 948 3730 srminfo@nist.gov	Mass fraction	98.9 %	0.2 % Level of confidence 95 %
cortisol	human serum	ERM-DA192, cortisol in human serum	JRC (European Commission, Joint Research Centre), European Union Phone : +32 (0) 14 571 705 Fax : +32 (0) 14 590 406 jrc-rm-distribution@ec.europa.eu	Amount-of-substance concentration	273 nmol/l	6 nmol/l Level of confidence 95 %
cortisol	human serum	ERM-DA193, cortisol in human serum	JRC (European Commission, Joint Research Centre), European Union Phone : +32 (0) 14 571 705 Fax : +32 (0) 14 590 406 jrc-rm-distribution@ec.europa.eu	Amount-of-substance concentration	763 nmol/l	14 nmol/l Level of confidence 95 %
cortisol	human serum	ERM-DA451/IFCC, cortisol reference panel	JRC (European Commission, Joint Research Centre), European Union Phone : +32 (0) 14 571 705 Fax : +32 (0) 14 590 406 jrc-rm-distribution@ec.europa.eu	Amount-of-substance concentration	83 nmol/l to 764 nmol/l	4 nmol/l to 29 nmol/l Level of confidence 95 %

Database of higher-order reference materials, measurement methods/procedures and services

JCTLM
Accurate results for patient care

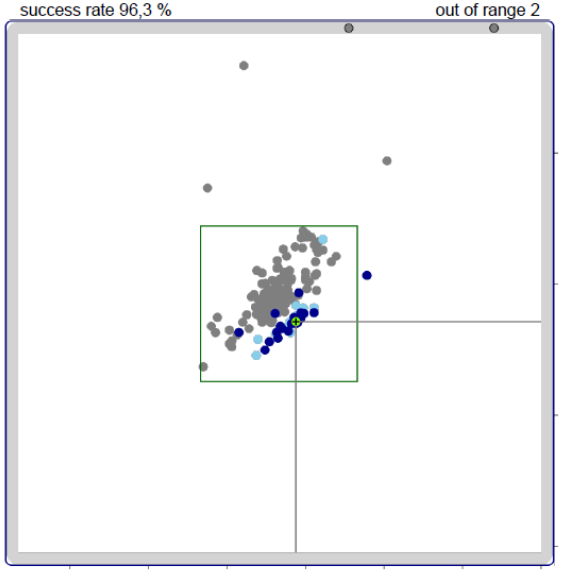
Isotope dilution mass spectrometry method for free thyroxine in blood serum

- University of Ghent reference measurement procedure for free thyroxine in serum

Applicable matrice(s)	lyophilized, fresh, or frozen serum
Full description of technique(s)	equilibrium diaysis ID/LC/MS
Quantity	Amount-of-substance concentration
Applicable range	1.8 pmol/L to 80 pmol/L
Expected uncertainty (level of confidence 95%)	6.9 %
Reference(s)	*Clin. Chem. Lab. Med.*, 2011, **49**(8), 1275 - 1281
JCTLM DB identification number	C8RMP1

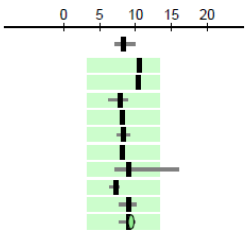
Analyte **17-OH-progesterone**
Method all methods

success rate 96,3 % out of range 2



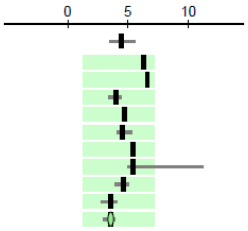
Sample A (RMW = 8.28 nmol/l)

M	Kit	N	Min	16.P	50.P	84.P	Max
Alle		164	3.48	7.19	8.37	10.0	22.0
1	53	7	8.79		10.6		11.1
1	99	5	9.73		10.4		10.8
1	111	19	3.48	6.28	7.88	8.98	10.7
2	35	7	7.51		8.10		8.38
2	41	49	6.54	7.45	8.36	9.14	12.8
2	49	7	4.27		8.20		10.7
2	99	9	6.91	7.11	9.09	16.0	22.0
4	23	8	6.00	6.32	7.24	7.79	8.06
10	47	9	6.88	7.77	9.03	10.1	10.5
10	99	18	5.75	7.71	9.00	9.90	13.9



Sample B (RMW = 3.22 nmol/l)

M	Kit	N	Min	16.P	50.P	84.P	Max
Alle		164	1.85	3.50	4.43	5.62	17.6
1	53	7	3.33		6.30		6.90
1	99	5	6.33		6.61		6.79
1	111	19	1.85	3.36	4.00	4.48	4.80
2	35	7	3.94		4.69		5.09
2	41	49	3.55	4.12	4.58	5.30	16.8
2	49	7	3.15		5.40		6.79
2	99	9	4.67	4.96	5.42	11.2	17.6
4	23	8	3.55	3.92	4.62	5.02	5.03
10	47	9	2.27	2.80	3.56	4.13	4.18
10	99	18	2.48	2.95	3.53	3.91	5.33



The deviation of your results from the median of the corresponding sub-collective (kit) is:
A 4.3 %
B 1.1 %

Other kits (number):
1-13(2), 1-24(1), 1-41(1), 1-44(1), 1-143(2), 1-211(1), 2-30(1), 2-36(2), 2-42(2), 2-53(1), 2-111(2), 2-270(1), 4-30(1), 4-41(1), 10-91(2), 10-134(2), 11-99(2), 11-335(1),

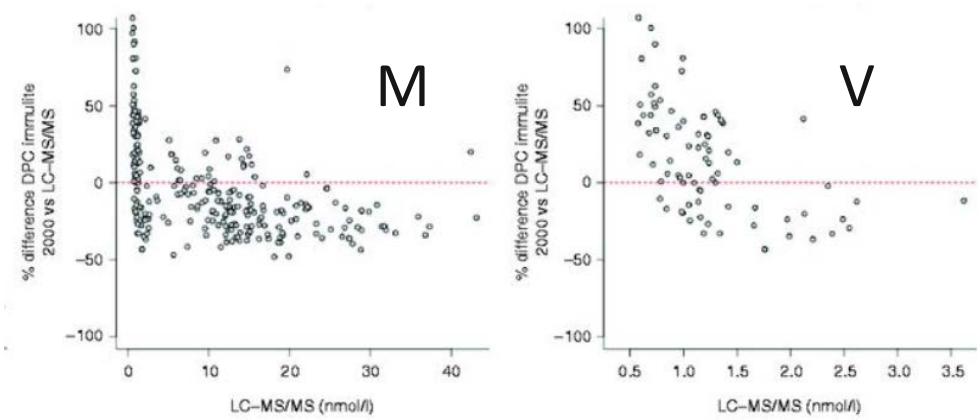
RfB Referenzinstitut für Bioanalytik

Referenzinstitut für Bioanalytik

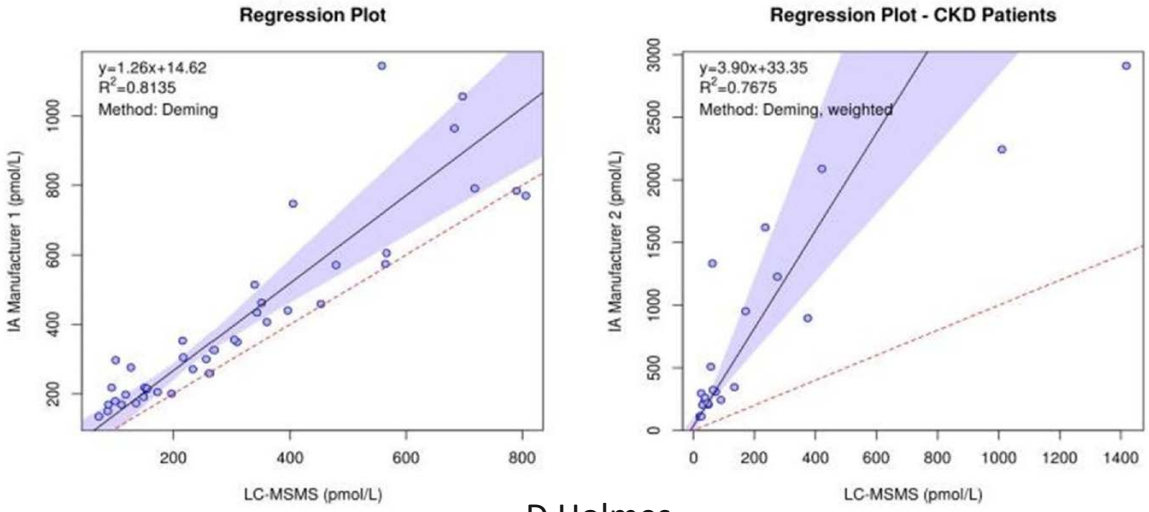
Is het daarmee opgelost?.....deels/nee

- Kruisreactie:
  - steroid metabolieten
- Interferentie:
  - Bindingseiwitten
  - (zwangerschap; TBG)
  - Medicatie

Testosteron difference plot
Immunoassay vs LCMSMS



Aldosteron in pat. met/zonder CKD

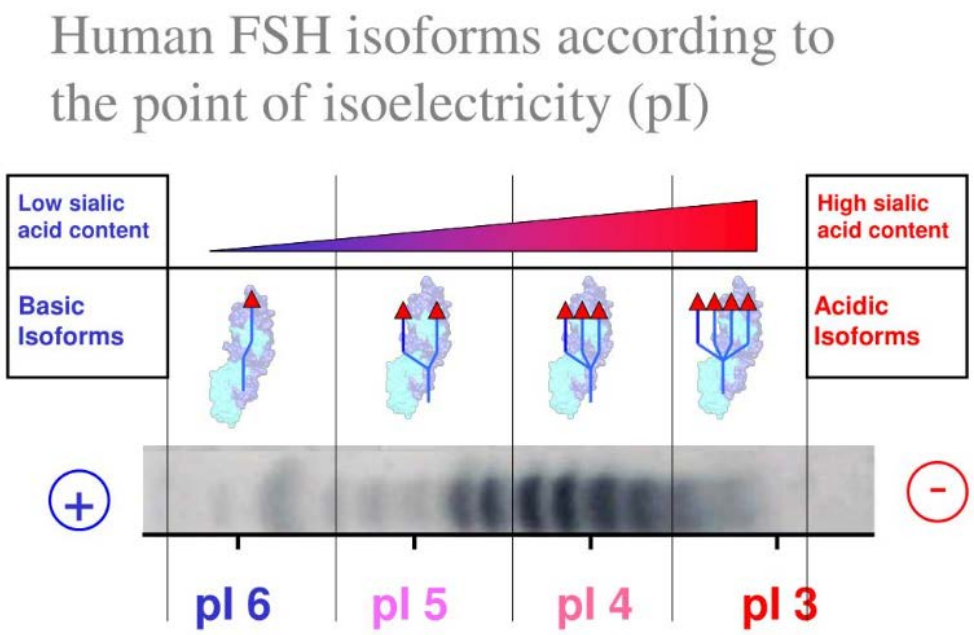


D.Holmes

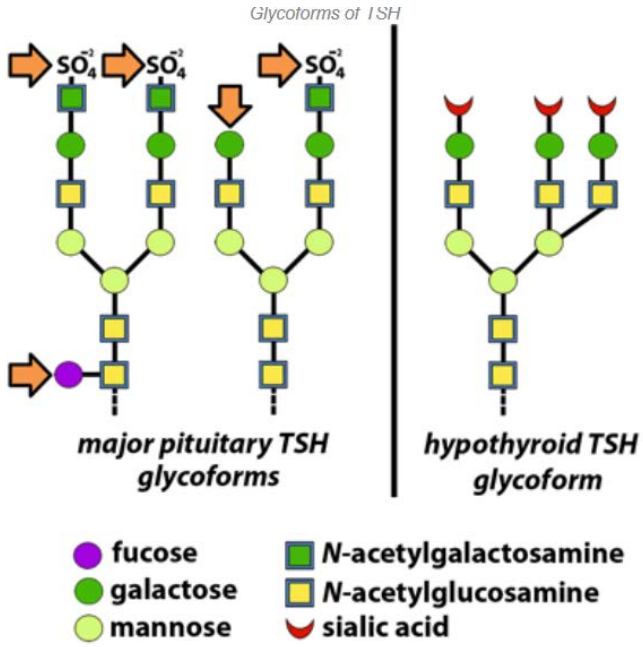
2. Wat minder “gemakkelijke” hormonen

Peptide hormonen: LH, FSH, ACTH, TSH, PTH, GH, insuline,…

- Isovormen
- Glycosyleringen
- Antistof gevoeligheid voor isovormen



TSH glycoforms



James D. Faix, MD, and Linda M. Thienpont, 2013

Insuline: geen isovormen/glycosylering

Table 2. Insulin values (µU/mL) and linear regression (Deming method) between each insulin assay and the mean of all assays.

			Each assay (y_a) vs. mean of 8 assays (a_8) [y_a = slope (mean a_8) + intercept]		
	Mean ± SD	Median (IQR)	Slope	Intercept	*r*
Roche, ECLIA	19.44 ± 16.67	14.71 (9.22–22.95)	1.243	−0.595	0.992
DiaSorin, CLIA	18.17 ± 14.54	14.00 (9.80–21.00)	1.085	0.695	0.974
Tosoh, IEMA	14.89 ± 13.47	10.80 (6.90–16.55)	1.003	−1.265	0.982
Mercodia, IEMA	15.85 ± 13.90	12.53 (8.00–17.77)	1.035	−0.818	0.986
Monobind, IEMA	16.14 ± 14.88	11.46 (6.92–20.88)	1.110	−1.740	0.980
Diametra, IEMA	11.66 ± 10.29	8.35 (4.53–15.98)	0.753	−0.476	0.940
Izotop, IRMA	18.31 ± 15.01	12.50 (9.10–22.07)	1.122	0.240	0.967
BioSource, IRMA	14.42 ± 13.10	8.53 (6.33–18.18)	0.971	−1.222	0.844

IQR: interquartile range; ECLIA: Electrochemiluminescence immunoassay; CLIA: Chemiluminescence immunoassay; IEMA: Immunoenzymometric assay; IRMA: Immunoradiometric assay. *r*: Pearson correlation coefficient.

Toch variatie tussen methoden:

Matrix

Pro-insuline kruisrx

Reagentia

Std zuiverheid

SCANDINAVIAN JOURNAL OF CLINICAL AND LABORATORY INVESTIGATION, 2017
VOL. 77, NO. 2, 122–129
http://dx.doi.org/10.1080/00365513.2016.1278260

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Assay-dependent variability of serum insulin concentrations: a comparison of eight assays

Maryam Tohidi[a], Parvaneh Arbab[a] and Asghar Ghasemi[b]

Harmonisatie mogelijkheden: bv TSH

Clinical Chemistry 63:7
1248–1260 (2017)

Endocrinology and Metabolism

Harmonization of Serum Thyroid-Stimulating Hormone Measurements Paves the Way for the Adoption of a More Uniform Reference Interval

Linda M. Thienpont,[1,2*] Katleen Van Uytfanghe,[3] Linde A.C. De Grande,[1] Dries Reynders,[4] Barnali Das,[5] James D. Faix,[6] Finlay MacKenzie,[7] Brigitte Decallonne,[8] Akira Hishinuma,[9] Bruno Lapauw,[10] Paul Taelman,[11] Paul Van Crombrugge,[12] Annick Van den Bruel,[13] Brigitte Velkeniers,[14] and Paul Williams[15] on behalf of the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT)

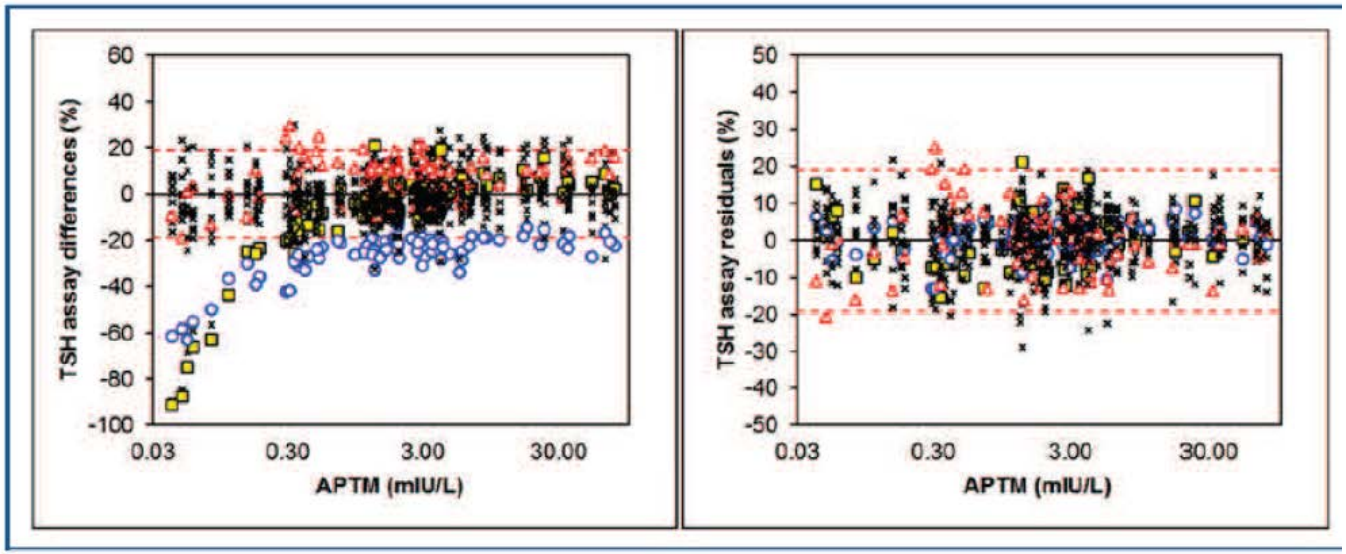


Figure 5: %-Difference plot from the APTM before and after harmonization of TSH assays.

From Thienpont report to C-SFT and FDA (APTM AA procedures Trimmed mean)

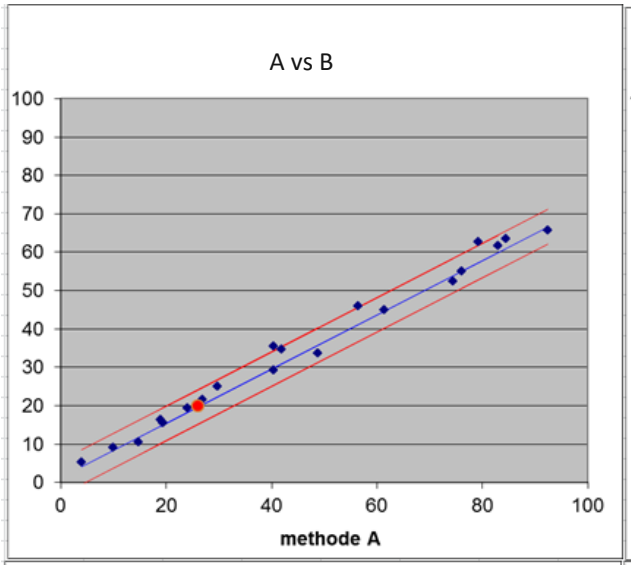
Expertwaarden toekennen

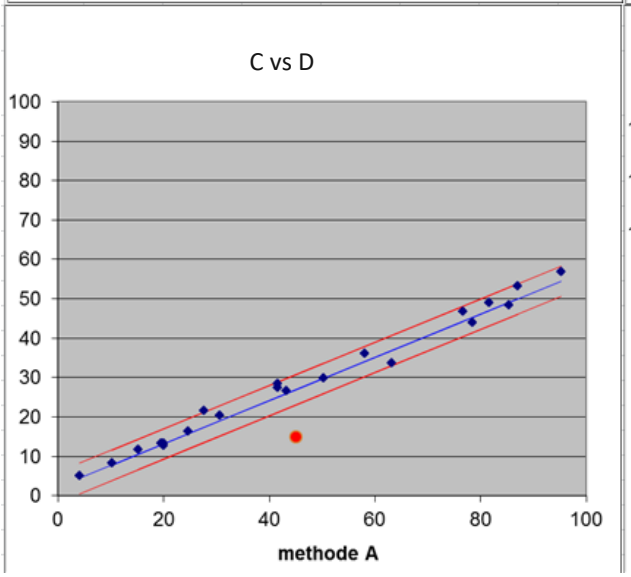
- Voorwaarden
  - Bij voorkeur natieve monsters gebruiken in de rondzendingen
  - Eventuele toevoegingen moeten “natuurlijk” zijn qua glycosylering/isovorm verhouding
  - Gebruikte rondzendmonsters moeten commuteerbaar zijn
  - Als expertwaarde:
    - ALTM
    - Vastgestelde mediane waarde van één of meer harmonisatiemonsters
    - Relateren aan de internationale standaard

- SKML: GH en IGF-1
  - Harmonisatiemonster met expertwaarde = mediaan van 3 rep. 4 methoden.

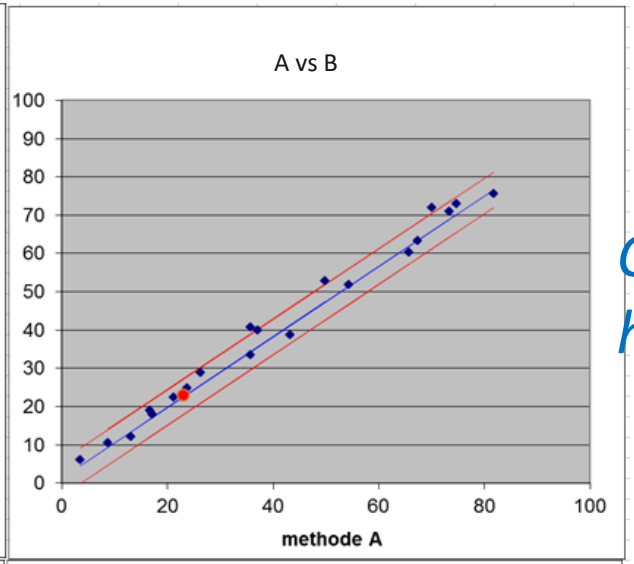
Commuteerbaarheid calibrator essentieel

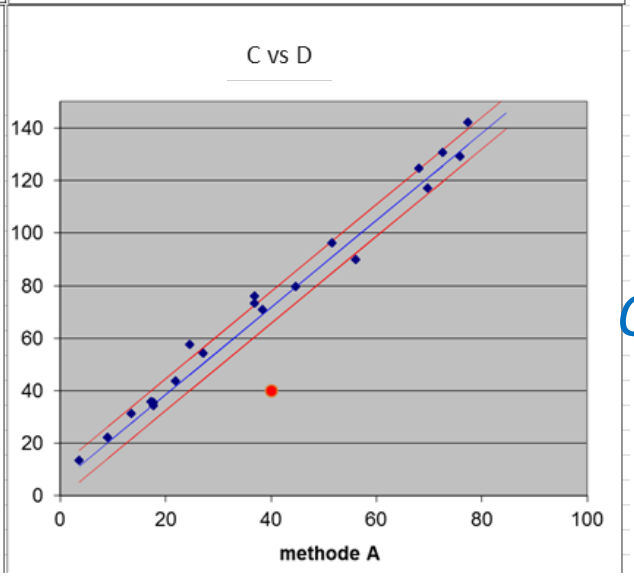
Voor





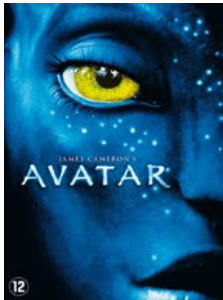
na correctie





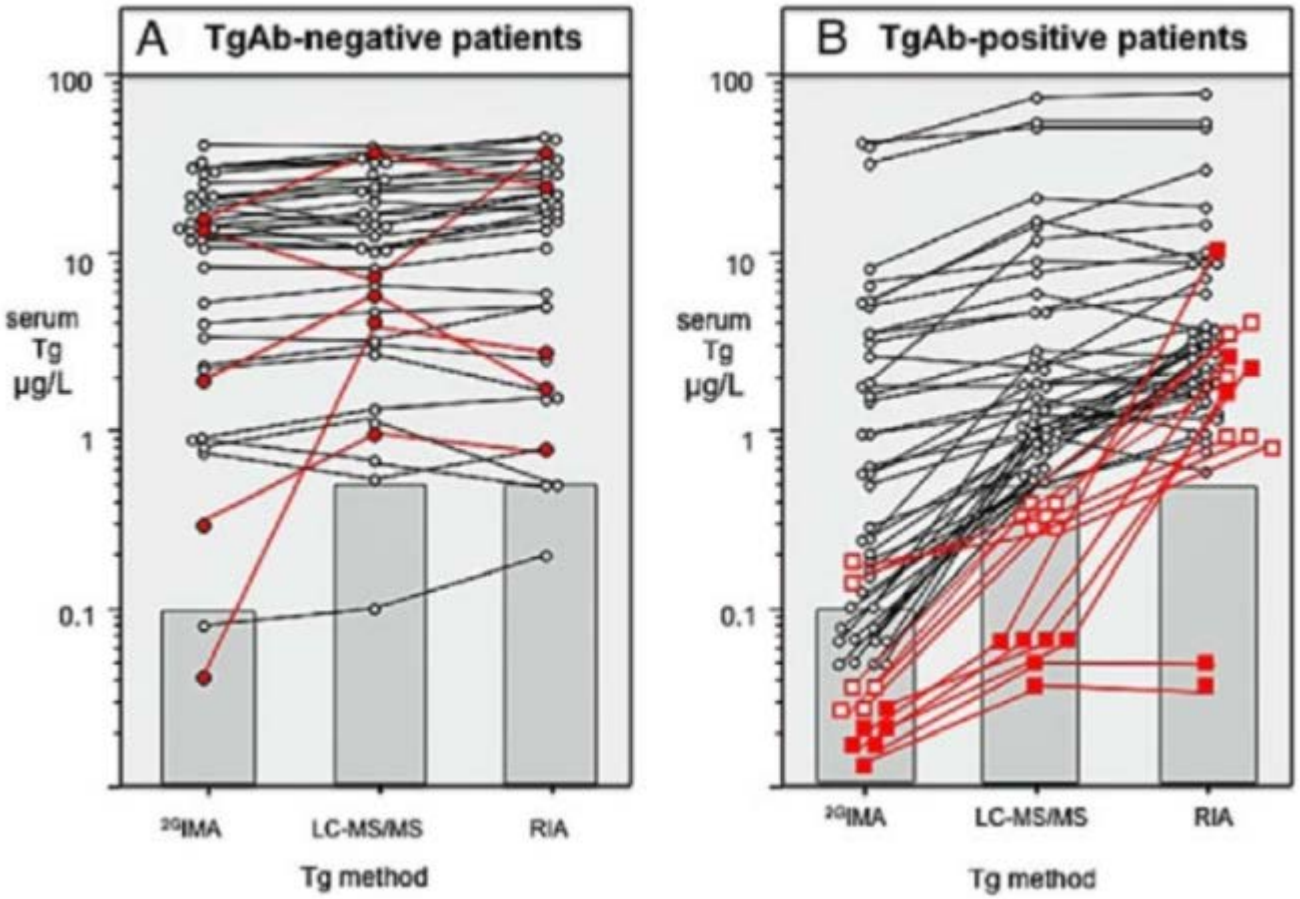
Correctie na harmonisatie

Overcorrectie



3. Moeilijk te harmoniseren: bv tumormerkers

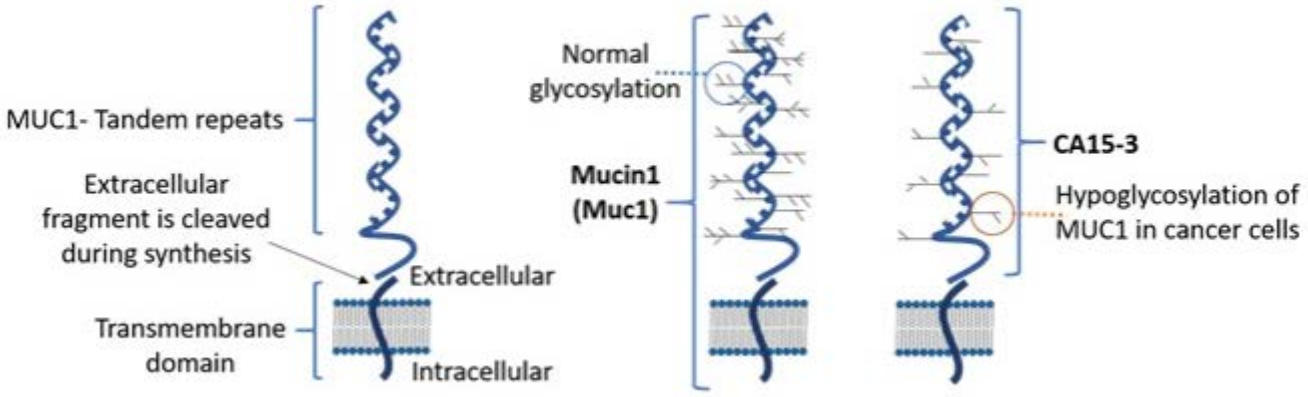
Figure 7. Serum Tg Measurements in DTC Patients with Structural Disease



A: Rood: >30% verschil tussen methoden
B: ☐: marginale TG waarden (LCMS) en ■ TG < FS van LCMS

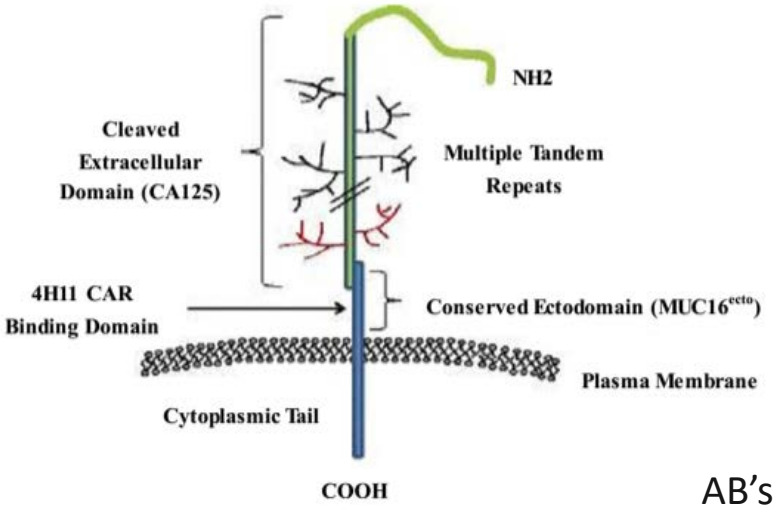
C. Spencer

Veel variatie in epitopen



CA15.3
= Muc 1

AB's DF3 en 115D8



Muc 16: bevat sterk geglycosyleerd CA125 domein

AB's: three groups, OC125-like (group A), M11-like (group B), and Ov197-like

Expertwaarden in de praktijk

➢ GH en IGF-1: harmonisatiemonster

Voor de GH en IGF-1 expertwaarden worden alle SKML monsters inclusief het harmonisatiemonster in duplo gemeten door vier verschillende laboratoria (m.b.v. iSYS, Immulite (GH), Liaison en Cobas apparatuur).

mediaan = expertwaarde

➢ 25OH vitamine D

Voor de vit D expertwaarden worden alle SKML monsters van 2019 gemeten middels LC-MS/MS methode door vier verschillende laboratoria.

mediaan = expertwaarde

Various calibration procedures result in optimal standardization of routinely used 25(OH)D ID-LC-MS/MS methods. Niek F. Dirks, Hubert W. Vesper, Antonius E. van Herwaarden, Jody M.W. van den Ouweland, Ido P. Kema, Johannes G. Krabbe, Annemieke C. Heijboer, Clinica Chimica Acta 462 (2016) 49–54

In voorbereiding

Projectvoorstel sectie Endo SKML

Maken van getargete calibratoren ten behoeve van de harmonisatie van de steroïden aldosteron, androsteendion, cortisol, testosteron, 17OH-progesteron en van FT4 en 25OHVitD.

- Maken calibratoren
- Commuteerbaarheid testen
- Mbv referentiemethoden vaststellen waarden

Conclusie: expert/target waarden toekennen?

- G
  s
- Bi
  g erbare
  ca en
- Bi G e.d.:
  w

That’s all