Progress in Standardization of Thyroid Function Tests

Linda M Thienpont, PhD, Prof. Em. Ghent University

Chair of the IFCC C-STFT

www.ifcc-cstft.org

Linda.Thienpont@ugent.be

Current affiliation
Thienpont & Stöckl
Wissenschaftliches Consulting GbR
EMPOWERIVD•GLOBE

IFCC Working Group/Committee for Standardization of Thyroid Function Tests (C-STFT)

Terms of reference

Develop reference measurement systems for free thyroid hormones and TSH

Establish a network of competent reference laboratories

Liaise with key stakeholders to implement traceable methods in routine clinical practice

http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft

Collaborating IVD manufacturers

Reference measurement system for FT4

FT4 reference measurement procedure

International "conventional" reference measurement procedure: Equilibrium dialysis (ED) combined with ID-LC/tandem MS (calibrated with the IRMM 468/469 primary reference materials)

Operational definition of the "measurand" FT4

"Thyroxine in the dialysate from ED of serum prepared under defined conditions (37°C; pH = 7.4; buffer, etc.)" (pmol/L)

Reference measurement system for TSH

TSH analysis is “mixture” analysis

Serum TSH – intact, total, with glycosylation pattern encountered in specified diagnostic applications

Results in mIU/L defined by WHO IRP 80/558 & 81/565

“The” problem

WHO IRP’s not commutable with TSH assays

Reference measurement procedure technically not to expect in the short- to midterm

Reference measurement system for TSH

Solution to the problem

“Harmonization” instead of standardization

“Surrogate” reference measurement procedure

Statistical “all-procedure trimmed mean” (APTM) inferred with a robust factor analysis model (caveat: correlation)

Method comparison with a clinically relevant panel

Follow-up panels all linked to the 1st harmonization panel

Requirements for success of standardization/harmonization

Sufficient intrinsic quality of the assays

“Step-up” approach until technical recalibration

Infrastructure for procurement of follow-up panels

Careful preparation of implementation

“Post-standardization” monitoring that the accomplished standardization status is sustained

Current status of the C-STFT activities

Phase IV method comparison studies for FT4 & TSH

Two panels of clinically relevant samples (n ~ 100)

FT4: 4.5 – 164 pmol/L (by ED-ID/LC/tandem MS)

TSH: ~ 0.002 to 75 mIU/L (APTM)

Inclusion of master calibrators

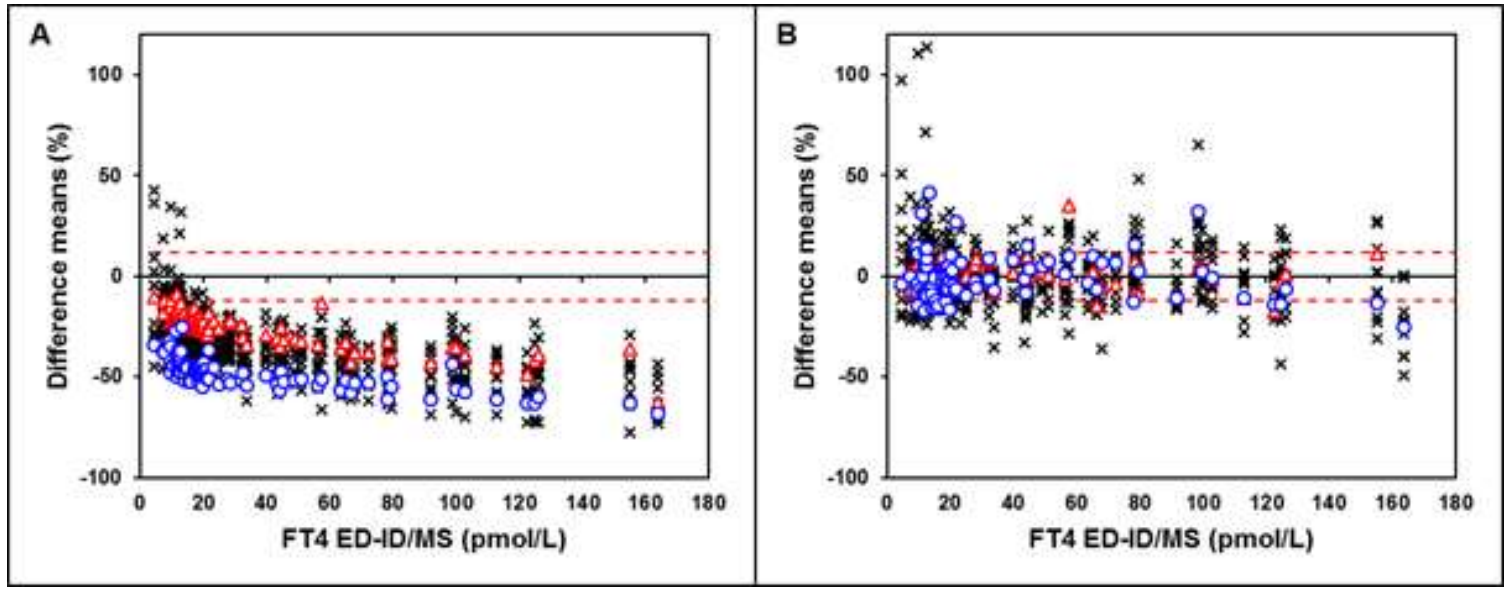
Recalibration by IVD manufacturers

Proof-of-concept (in process)

Two panels (n ~ 120) measured for FT4 and TSH

Phase IV – Outcome

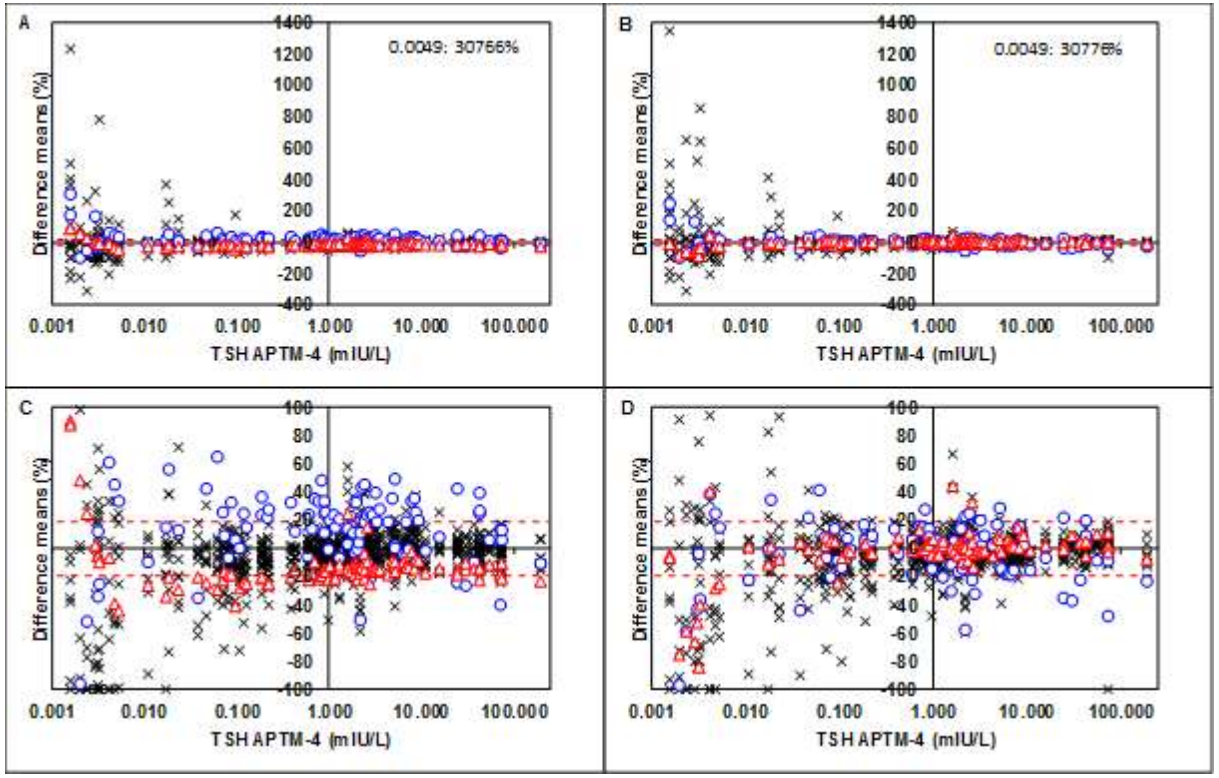
FT4 before (A) and after (B) recalibration



Before : all assays strongly negatively biased
After : bias to ED ID-LC/tandem MS removed

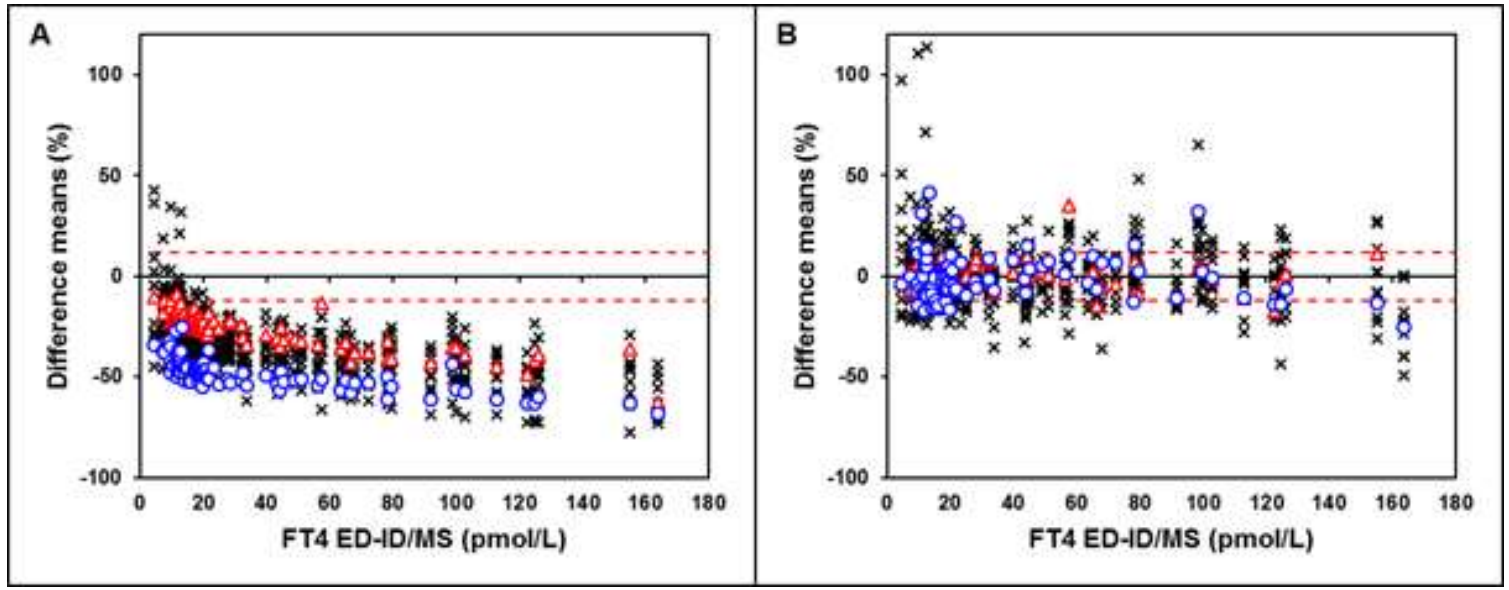
Phase IV – Outcome

TSH before (A) and after (B) recalibration



Phase IV – Outcome

Huge impact of FT4 standardization



Impact of TSH harmonization reasonable

Preparation of implementation

Liaise with regulatory authorities

Liaise with key stakeholders

Do benefit-risk analysis at all levels of stakeholders

Educate stakeholders about impact/changes

Coordinate global implementation of recalibrated assays

Benefit-risk analysis

Benefits

Common reference intervals/clinical decision limits

Aggregation of results from several studies

Evidence-based clinical practice guidelines for application of consistent standards of medical care

Translation of research into patient care & disease prevention

Electronic patient records with inclusion of laboratory data

➔ Benefits generally recognized

Risk analysis

Potential risks

Mainly related to impact of standardization/harmonization

Actions needed to mitigate potential risks

Manufacturers: duly communicate on recalibration

Laboratories: properly inform about changes in reports

Clinicians: accommodate for changes in diagnostic and patient monitoring strategies

Patients: should not be confused; avoid non-compliance

Actions to mitigate risks

Establish an interface and discussion platform with all involved stakeholders

Look into the information chains used by the resp. parties

Send questionnaires/case studies and evaluate

Attend scientific meetings (face-to-face contact)

IVD manufacturers, laboratory- and clinical community

➔ **Minimal risks anticipated because it is very unlikely that the well communicated changes will not be captured**

Actions to mitigate risks

Call for input on benefit-risk analysis

Thienpont LM, Faix JD, Beastall G. Standardization of FT4 and harmonization of TSH measurements - a request for input from endocrinologists and other physicians/International Thyroid Foundation.

- Clin Endocrinol (Oxf) 2015 Jul 23. [Epub ahead of print].
- Endocr J 2015; 31;62(10):855-6.
- Exp Clin Endocrinol Diabetes 2016;124:61-2.
- Thyroid 2015;25:1379-80.
- Endocrine 2015;50:826-7.
- Eur Thyroid J 2015;4:217-2
- Endocrine Pract 2016 [in print]
- Sent by e-mail to relevant members from the ESE
- ThyroWorld 2015;18:13-4.

Post-standardization monitoring of accomplished standardization status

The “Percentiler” and “Flagger” applications

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Real-time monitoring of patient medians from individual laboratories using different IVD test systems

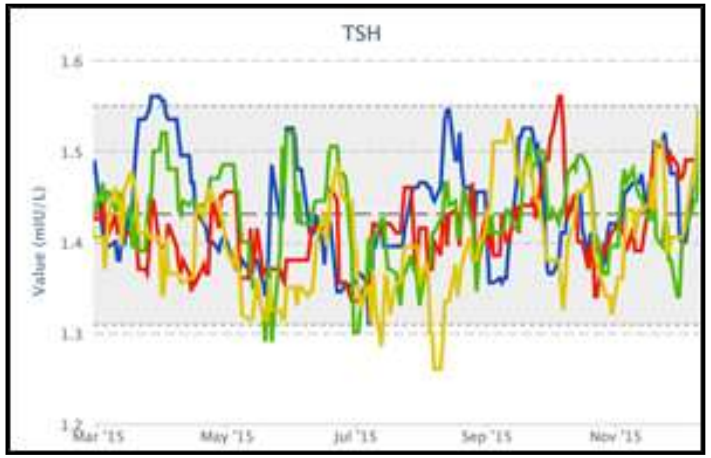
➔ Global evidence base on IVD test stability against realistic quality specifications across laboratories & peers/manufacturers

Real-time monitoring of flagging of results against reference intervals or decision limits

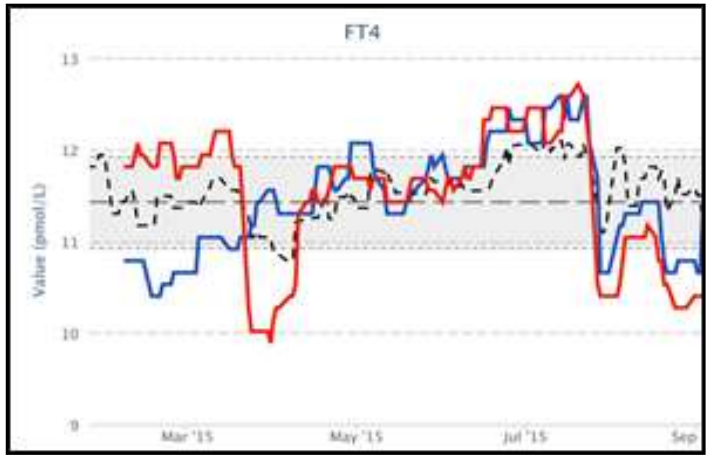
➔ Effect of analytical instability on “surrogate” medical decisions

Relevant examples of stability monitoring with the Percentiler

Good stability



Shifts



Saw-tooth pattern

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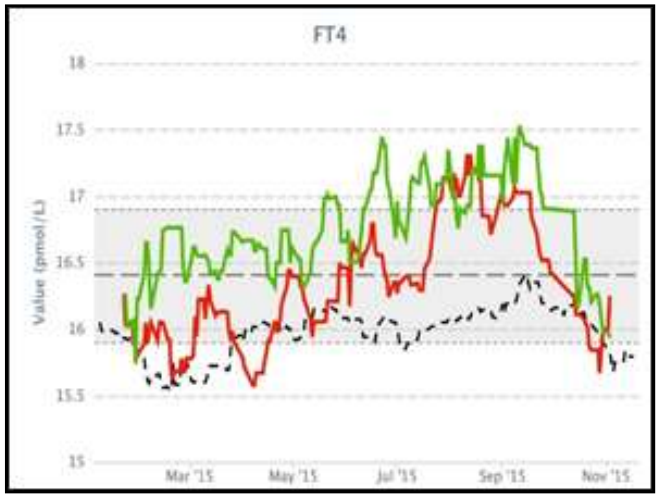
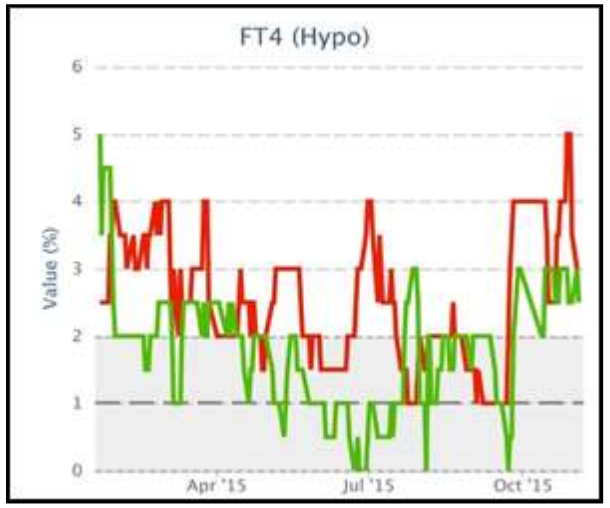
Percentiler and Flagger link

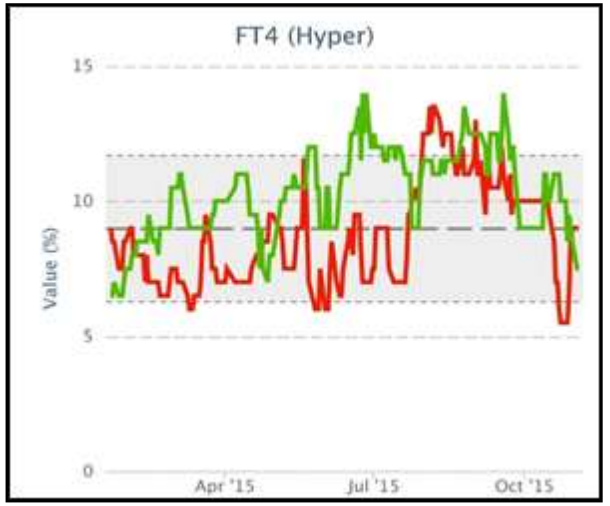
Percentiler



Hypo-



Hyper flagging



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Final implementation

Coordination of global implementation of standardized/harmonized assays

Timelines?

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Linda Thienpont

Linda.thienpont@ugent.be