**Progress in Standardization of Thyroid Function Tests**

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On behalf of the IFCC-C-STFT  
Chaired by Prof. Dr. Linda Thienpont  
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**Economic impact of thyroid testing**

High burden on the healthcare system  
Yearly 10^10 TSH & 60*10^9 FT4 tests performed worldwide  
Testing volume might even increase  
For example, recent meta-analysis links subclinical thyroid dysfunction to coronary heart disease & “all-cause” mortality#  


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**IFCC Working Group/Committee for Standardization of Thyroid Function Tests (C-STFT)**  
Chair: Prof. Dr. L. Thienpont

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/ad-committees/c-stft/

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**Disclosure**

Support to the UGent  
Abbott Diagnostics (Abbott Park, IL, USA)  
Beckman Coulter, Inc. (Brea, CA, USA)  
bioMerieux s.a. (Marcy-l’Etoile, France)  
DiaSorin S.p.A. (Saluggia, Italy)  
Fujirebio Inc, (Tokyo, Japan)  
Mindray Medical International Limited (Shenzhen, China)  
Ortho-Clinical Diagnostics (Rochester, NY, USA, Buckinghamshire, UK)  
Roche Diagnostics GmbH (Mannheim, Germany)  
Shenzhen New Industries Biomedical Engineering Co., Ltd (SNIBE Co., Ltd, Shenzhen, China)  
Sichuan Maccua Biotechnology Co., Ltd (Chengdu, China)  
Siemens Healthcare Diagnostics Inc. (Deerfield, IL, USA)  
Tosoh Corporation (Tokyo, Japan)

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**Benefits of using standardized assays**  
Fit to address modern clinical & public health needs  
- Common reference intervals/clinical decision limits  
- Evidence-based clinical practice guidelines  
- Application of consistent standards of medical care  
- Translation of research into patient care & disease prevention activities  
- Electronic patient records  

- Whether these needs can be met, depends on the availability of laboratory results that are comparable over time, location & across assays

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**Development of a reference measurement system for FT4**
Definition of the “measurand” FT4

IUPAC/IFCC format#

Component
Thyroxine (free)

Kind-of Quantity; units
amount-of-substance concentration (pmol/L)

System
Plasma/Serum under physiological conditions (pH 7.4, 37°C)


FT4 reference measurement procedure

International conventional reference measurement procedure (RMP)# based on

• Equilibrium dialysis (ED)
• Quantification of thyroxine in the dialysate with a “trueness-based” reference measurement procedure ➔ ED-ID-LC/tandem MS

NOTE
The measurand is operationally defined as “Thyroxine in the dialysate from ED of serum prepared under defined conditions”


Development & validation


Development of a reference measurement system for TSH

TSH reference material & -procedure

The problem

• IU defined by a WHO standard
• WHO IRP 80/558 (also 81/565) mixture components differ from those in serum; they, therefore, do potentially not give the same dose/response in immunoassays as TSH in its natural environment ➔ Are not commutable and not suited for standardization


Dr. K. Van Uytfanghe
### TSH harmonization approach

**Proposal by C-STFT**
- Statistical "all-procedure trimmed mean" (APTM)
  - From a method comparison with a clinically relevant panel
  - With participation by (as many as possible) assays
  - Serves as "surrogate RMP"1

**NOTE**
- Statistical basis: robust factor analysis model2
- Requires excellent correlation of results to the APTM

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### "Step-up" approach

**Second step-up to standardization/harmonization**
- Method comparison with a new clinically relevant panel
- Technical recalibration of IVD assays

**Phase after standardization/harmonization#**
- Procure a follow-up panel
- Assess sustainability of the status after technical recalibration of IVD assays (= risk analysis implied by the FDA)#
- Prepare implementation of standardization/harmonization

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### Requirements for standardization/harmonization

**"Step-up" approach#**

- Method comparison with high-volume sera from "apparently healthy" volunteers
- Assessment of assays' basic performance attributes
- Mathematical recalibration

**First step-up2**
- Method comparison with a clinical panel and inclusion of master calibrators
- Verification that assays perform similarly on clinically relevant samples
- Recalibration by IVD manufacturers

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### Current status of standardization of FT4 and TSH assays

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**Standardization status – FT4**

Phase III – Bias to ED ID-MS®
- 9–27 pmol/L: -25% (mean)
  - Range: -1% to -42%
- >27 pmol/L: -37% (mean)
  - Range: -21% to -48%
- <9 pmol/L: 2% (mean)
  - Range: -26% to 62%

→ All assays strongly negatively biased


![Image](image1.png)

**Standardization status – TSH**

Phase III – Bias to APTM#
- TSH concentration range of the panel: 0.04 – 80 mIU/L
  - <0.3 mIU/L: comparability quite good; only 2 assays differ by >10% from APTM
  - <0.5 mIU/L & >5 mIU/L: max 5 out of 14 assays outside the ±10% limit
  - Max discrepancy between assays up to ~33% (whole range)


![Image](image2.png)

**Feasibility of standardization/harmonization**

Feasibility of standardization/recalibration

**FT4 – Phase III#**

→ Bias to ED ID-LC/tandem MS removed
→ Residual dispersion nearly entirely due to within-assay effects


![Image](image3.png)

**Feasibility of standardization/recalibration**

**TSH – Phase III#**

→ Recalibration nicely centers the distribution of the assay differences around zero
→ Remaining dispersion from within-assay effects
→ Indirect proof of glycosilation blind assays


![Image](image4.png)

**Current status of project and way forward**

- Dr. K. Van Uytfanghe
Step-up to standardization/harmonization

Phase IV method comparison study
- New clinically relevant panels, measured in parallel with master calibrators:
  - FT4: 4.5 – 164 pmol/L (by ED-ID/MS), n = 91
  - TSH: −0.002 to 75 mIU/L (APTM), n = 101
- Measurements done
- Preliminary report discussed with the IVD manufacturers
- Final data treatment on-going
- Recalibration by manufacturers to follow

Preparation of follow-up panels
- TSH panel ready (and targeted)
- FT4 panel collected (will be targeted)

Proof-of-concept

Reference interval (RI)
- Panel of 120 samples from apparently healthy Americans to be measured by recalibrated assays
- FT4 target values are currently set by ED-ID/MS at UGent

- Proof-of-concept for success of standardization/harmonization and feasibility to use a common RI
- Basis for further establishment by manufacturers of new RIs after standardization/harmonization

Implementation

Obstacles to implementation

Impact of standardization

Most pronounced for FT4 testing
- Effect mainly in the eu- & hyperthyroid range
- Measurement values will increase in general by 30 – 50%
- Reference intervals will change

Measures to waive obstacles

Prior to implementation
- Liaise with regulatory authorities
- Liaise with key stakeholders
- Do risk-benefit analysis at all levels of stakeholders
- Educate stakeholders about impact/changes
- Coordinate implementation of standardized/harmonized assays by all manufacturers at the same point in time and worldwide
- Monitor sustainability of standardization status

Collaborating IVD manufacturers

- Abbott
- Biorad
- BioMérieux
- DaSand
- Fujifilm
- Maccra
- Mindray
- Ortho Clinical Diagnostics
- Roche
- Siemens
- SiMbe
- Toky

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