

**IFCC Working Group on Standardization of Thyroid Function Tests (WG-STFT)**  
**Meeting at AACC 2010, Anaheim, CA, Monday July 26<sup>th</sup> (2:00 - 5:00 pm)**

**PARTICIPANTS**

The meeting attendance list is attached in annex.

**OPENING OF THE MEETING**

The chair welcomed the meeting attendees and proposed to make a roll call. She spoke a particular word of welcome to Dr. A. Gutierrez (accompanied by 2 members of his staff) from the Food and Drug Administration (FDA), because he had been so kind to accept her invitation. His attendance was of importance for the WG to clarify some concerns raised before by the participating IVD-manufacturers regarding acceptance of certain aspects of the project approach to calibration/standardization by the FDA.

The chair presented the agenda of the meeting. Two presentations would be held, one by herself and one by Prof I. Young, Vice-Chair of the IFCC Scientific Division (SD). The respective presentations are attached (Presentation-Thienpont.pdf; Presentation-Young.pdf).

**OBJECTIVES OF THE MEETING**

The chair explained that her presentation had the following objectives:

- Give the status report of the project and discuss the different achievements.
- Prepare and discuss the next phase III.
- Start the discussions about the future actions needed, with special attention to some concerns by the IVD-industry.

**STATUS REPORT**

*Finalization of Phase II (proof of concept)*

Phase II consisted of a second method comparison for FT4 and TSH, covering a broader concentration range (hypo-, eu- and hyperthyroid concentrations) than in the first study. It was also characterized by inclusion of the manufacturers' master calibrators. The underlying idea of the latter was to verify whether a similar post-calibration status could be achieved as in phase I, where mathematical recalibration was done. This was the case. An interesting observation in phase II was that TSH samples with elevated concentrations behave differently from those with euthyroid values with some of the assays. It was unclear whether this observation truly reflected a performance difference or was due to the matrix of the samples (to recall: the samples had been obtained from a commercial source, i.e., SeraCare). To exclude the latter, the chair had repeated the study with 30 clinical samples with high TSH values and 30 normal samples from one and the same center (the Academic Hospital of the Free University of Brussels, BE). Comparison of the results obtained with 2 assays, one that had shown a different performance in phase II, another that had not, allowed to conclude that the observation in phase II was most probably due to a matrix effect in the SeraCare samples. Upon contact with the vendor to identify the source of the matrix effect, it appeared that the company could not help, because of a lack of traceability of the samples. The chair, therefore, doubted about the opportunity to further collaborate with SeraCare.

*Publications*

The chair mentioned that the manuscripts on the 3 Phase I studies, recently published in Clinical Chemistry, apparently received a lot of interest. One of the IVD-manufacturers expressed his concern about the fact that some colleagues had asked the chair to reconfirm their code, most probably on demand of some customers. He considered this as a violation of the agreement on anonymous treatment of the results from phase I. The chair confirmed that she had respected the anonymity under all circumstances, but that she could not prevent when a manufacturer decided to disclose his codes. The liaison between the WG and the SD (Prof. L. Siekmann) said that it was the wish of the IFCC that all further studies should identify the manufacturers/assays. The chair replied that she understood that wish; however, she would need to discuss this with the participants prior to Phase III.

The chair presented and summarized some related Clinica Chimica Acta publications/manuscripts under revision by her research group (FT4 in pregnancy study performed together with a research group from the Academic Hospital of the Free University of Brussels; opinion paper on harmonization of protein measurements), as well as forthcoming ones, already submitted or to be submitted on behalf of the WG. One is a status report of Phase I and II, submitted to Clinical Chemistry and Laboratory Medicine, for a special issue dedicated to IFCC projects (revision 1 submitted). A second one is under preparation and will provide an extensive description of the ED ID-MS candidate international conventional reference measurement procedure (RMP) for FT4. This manuscript will be prioritized by UGent on special request from the SD, in order to put the method approval to ballot vote, so that it can formally be recommended by the IFCC (envisaged title: "IFCC Recommended International Conventional Reference Procedure for the Measurement of the Substance Concentration of Free T4 in serum"). UGent recently finished the last optimization and necessary investigations to show method robustness and independency of certain potentially confounding factors (brand and cut-off of dialysis membranes, generation of non-esterified fatty acids during dialysis, adsorption of T4 in standard solutions at pg/µL concentration, etc.). In addition, an intercomparison study with ReCCS (Japan) to prove the transferability of the method is ongoing and near finalization. The next step will be nomination of the RMP for listing by Joint Committee for Traceability in Laboratory Medicine (JCTLM).

#### *Involvement of clinicians*

In January 2010, a call to clinicians was done to solicit their interest in joining the WG activities/discussions, and to ask their help with the procurement of clinical samples for phase III/repository panels. A lot of interest was declared, however, the need to receive the approval by local ethical committees seemed a major obstacle to give support to the procurement of clinical samples. This was the reason why for Phase III the chair had decided to look again for a commercial source of clinical samples.

#### *Contacts with other societies - Dissemination of results*

The chair indicated that she had the intention to establish a first contact with the Endocrine Society through courtesy of Dr. W. Rosner. Meanwhile she had a good informal meeting with him, sent him all scientific information he asked for and is awaiting how the project will be received by the Endocrine Society. She also is in touch with the editor of Clinical Chemistry (Dr. N. Rifai) to help in dissemination of the results by making the link to other journals.

The chair proposed to limit for future publications the number of authors to a group of 3 to 4. The WG-members and other attendees agreed; however, the IVD-manufacturers asked that the chair would continue to circulate the papers before submission and the chair agreed to this.

### *Related matters*

The chair presented in short the TSH project of Prof C Ronin, which will be funded by the French National Research Agency. The WG looks forward to the outcome of the project.

### **PHASE III STUDY**

This study plans a new method comparison with clinical FT4 and TSH samples (note: “clinical” is to understand as samples from a “clinical setting” and covering the hypo-, eu- and hyperthyroid concentration range). It is intended to answer the question whether assay performance on samples with hypo- and hyperthyroid FT4 and TSH concentrations is identical to the performance on samples covering the euthyroid range. For FT4, this will be verified in relation to the RMP; for TSH, in relation to the ‘all-procedure trimmed mean’. If the assay performances are identical, standardization becomes possible. A second objective of Phase III is to extend the calibration to the full measurement range of the assays.

#### *Source and description of samples; technical aspects*

The chair has prepared Phase III already to a great extent. Through courtesy of Dr. R. Janzen she was brought into contact with the company PromedDX. As a result of the negotiations with the representative, Dr. J. Boushell, an offer was made for obtaining 2 sets of clinical samples, one with 90 samples for FT4 (30 eu-, 30 hyper-, 30 hypothyroid) and another with 100 samples for TSH (30 eu-, 30 hyper-, 40 hypothyroid). Supporting information including data on the samples, in- and exclusion criteria, storage and processing conditions, price quotation, delivery time had already been circulated before the meeting, to give the IVD-manufacturers and WG-members the chance to comment. The chair presented a positive reply by PromedDX on the amendments meanwhile requested by the WG members and project participants. In the meeting, 3 additional proposals were made: the use of only one blood tube (the most commonly used, red capped with gel separator); addition of an extra exclusion criterion: individuals with psychiatric disorders; need for providing the collaborating centers with a clear handling instruction from blood draw, to final aliquotting and long term storage and approved by the WG-STFT. Meanwhile, the chair added the demand for the specification of the Eppendorf vials to be used for aliquotting of the serum per 0.5 mL. The chair forwarded already the additional criteria to her contact person and is currently awaiting his reply,

The volume per sample will be 15 mL aliquotted per 0.5 mL. Because the required volume for FT4 analysis by ED ID-MS is 3 mL, the remaining volume for that panel will be 12 mL. This is a sufficient volume for at least 2 aliquots per participant (8 in total; 7 already positively replied, for 1 the reply is still pending). However, this will require that manufacturers of several assays/platforms decide which assay to include, or purchase an additional aliquot of the remaining ones (FT4: 8; TSH: 14).

#### *Measurement protocol*

As in the past, the measurement protocol and accompanying reporting template will be proposed and prepared by UGent, in consultation with the participants.

#### *Timeline*

In view of the fact that, after initiation of the project, PromedDX needs 10-15 weeks for the blood collections, the group agreed to start the Phase III measurements in February 2011.

#### *Comment and proposal by Dr. M Rottmann (Roche)*

Because of the FDA requirement that a calibration panel should cover 80% of the measurement range of an assay and the presumption that it will be extremely difficult to obtain very high FT4 concentrations, Dr. M. Rottmann had proposed to the chair to also include in Phase III 3 "spiked" samples. He proposed to spike at concentration levels of 30, 60 and 90 pmol/L. Measurement of these samples in parallel with the clinical samples would allow the participants to verify the commutability of the spiked samples with their assay. In the positive case, this would facilitate to cover the high end of the measurement range in the calibration/standardization panel. Roche proposed to prepare the samples in the last trimester of 2010. Samples would be distributed from UGent. This proposal was accepted. Finally, the FDA representatives were asked to confirm that the requirement 'calibration panel to cover 80% of an assay's measurement range' was valid and that the proposed approach with spiked samples was acceptable. The confirmations were received, however, in reply to the argument of the IVD-industry that nowadays it is difficult to find patients with extreme thyroid hormone concentrations because of faster diagnosis of thyroid disorders and treatment, Dr. Gutierrez argued that in spite of this, he observed that the measurement ranges of most assays were still very broad. He suggested that this should maybe be revisited by the IVD-industry.

## **DISCUSSION ABOUT THE FUTURE OF THE PROJECT**

### *Questions/concerns by IVD industry*

Although it was initially the intention to discuss the future of the project after the presentation of Prof. I. Young, the chair, knowing that Dr. Gutierrez was only able to attend part of the meeting, invited the IVD-manufacturers to take the opportunity to address their concerns, expressed in previous meetings, to the FDA representatives. One was whether harmonization of TSH measurements to the 'all-procedure trimmed mean' (to recall: according to the outcome of the TSH method comparison on samples from healthy individuals, the potential of this approach was recognized) would be acceptable for the FDA. IVD-manufacturers were concerned that this may result in the lose of current traceability to the WHO TSH reference preparation for some assays. The chair argued that it was her opinion that the traceability to the WHO would remain, because the only effect of the approach would be that the current harmonization status (to recall; 13 out of 16 assays agreed already within 10% limits) is tightened. She considered this goal worth achieving, in particular in view of the ongoing discussions on lowering the upper limit of the reference interval to a common decision value. Without going into a detailed reply, it was the opinion of one of the FDA representatives that any approach that improves the quality or fitness to purpose of an assay may be acceptable. Of course, the approach should be well documented. On the other hand, it was highlighted that currently traceability to the WHO is required by the European IVD-Directive. Manufacturers confirmed that it is indeed difficult for them to comply with the different international regulations. Another problem was raised, i.e., the difference in TSH isoforms or glycosylation patterns in the WHO standard versus serum panels, which can influence the decision-making process. The chair proposed to discontinue the discussion until the outcome of phase III was known, at which stage a discussion to decide on "go/not go" for the TSH harmonization approach will make sense.

### *Transformation of WG-STFT into Committee*

The chair indicated that within the SD there has been discussion about the transformation of the WG-STFT into a Committee. The rationale for this was that in view of the status currently achieved in the project (the technical part of the standardization process is accomplished or

at least in an advance stage), it is now the time to start with the development of a plan for implementation of standardization. In addition, the breadth of current objectives of the WG might be better addressed as an SD Committee. From this point of view, a Committee comprising a broader forum of colleagues would be a better platform to call upon the support and involvement of all stakeholders.

### **PRESENTATION BY PROF. DR. IAN YOUNG**

The Chair introduced Prof. Ian Young as guest speaker. He is Vice-Chair of the IFCC SD. The SD wanted him to express their view and expectations with regard to standardization of thyroid function testing.

Prof. Young stressed the importance of distinguishing between standardization and harmonization. Although either of the 2 approaches can be opted for, he asked the WG to carefully consider the advantages and disadvantages of each before proceeding. Also transparency about the selected approach and its sustainability should be assured. He continued with emphasizing the impact that standardization would have, which can be derived from the outcome of the first method comparison studies published in Clinical Chemistry. He underlined that on the basis of the huge impact for certain thyroid hormone measurements, sufficient attention will have to be paid to adapting reference intervals (RIs) and decision limits. This will require acceptance and understanding of the consequences of standardization by all involved parties (IVD-manufacturers, laboratories, regulators, clinicians, patients etc.). The group agreed with this point of view of the SD.

### **DISCUSSION**

The meeting was now open for questions and further discussions. The liaison between the SD and the WG suggested that the WG should consider the concordance of the observations made in the project with those in the German External Quality Control Scheme (EQAS). This scheme also evaluates assays/measurements against reference method values according to the Rilibäk regulations. The results are accessible on internet, however, because of the confidentiality of the project results, only the chair can do the verification. A discussion was started regarding the differences in matrix of the processed EQA samples versus the unadulterated samples in the project, which could be a potential source of divergence in outcome, and, a reason to deem this type of samples for accuracy/trueness assessment. This was confirmed by Prof. Siekmann, who, nevertheless, saw benefit in doing the exercise. Also the IVD industry was interested, because after all, they have to satisfy customers who have to pass the German EQA. This comparison could occur in 2 phases, first investigate whether there is concordance or divergence; in the latter case try to offer a solution to this problem. A major issue for e.g. TSH will of course be whether the divergence is due to processing of the EQA material or a difference of the analyte in the material in comparison to in a native samples. The chair was of the opinion that solving this issue did not belong to the task of the WG. Nevertheless, the WG considered it important not to forget that EQA-organizers should be involved in the implementation plan of standardization.

From the side of the clinicians, the question was repeated to disclose the identity of the assays/manufacturers in future reports. They claimed that manufacturers should not be reluctant to do so, because nowadays the quality of IVD-assays is quite similar, so that none would be harmed by more transparency. Manufacturers proposed to consider this request within the higher hierarchy of their company.

The WG stressed the importance of education and inclusion of primary care doctors and patient groups in the implementation plan. This is because patient safety and re-gaining

confidence in the reliability of thyroid testing should be an overarching goal of this IFCC project.

It was questioned by some colleagues from the audience why very ill patients were excluded from Phase III. The chair mentioned that manufacturers had proposed this in the discussion last year. They considered the clinical relevance of results for this patient category low and referred to the fact that even the NACB guidelines discourage to measure thyroid hormones in those patients. Some attendees argued that, nevertheless, there may be cases where thyroid testing makes sense. The chair asked to confirm the correctness of her impression from literature that in very ill patients FT3 and reverse T3 was of more clinical relevance than FT4. Prof. C. Spencer and Dr. O. Soldin denied this. The WG concluded that assessing the quality of their FT4 assays for this application would be very challenging, but proposed that the clinical samples as planned for Phase III should be prioritized.

Another discussion subject was the implementation of specific RIs for FT4 during pregnancy. In answer to this, the concern was raised that laboratories are not used to work with different reference ranges for one and the same analyte, and that it could cause major confusion of clinicians and patients. Also the fact of ethnic differences in RIs was raised, and therefore, the difficulty of establishing reliable RIs from large populations, and even more, of assuring that the laboratory uses the correct ranges for its patient populations. Some raised the remark that there is also a general physiological component at the basis of the differences in FT4 seen in pregnancy, which enlarges the problem. This discussion should be raised again in a later phase.

## **CONCLUSION**

When no further questions were posed, the chair thanked the audience for their contribution to the meeting. She promised to contact PromeddX with regard to the new amendments requested and to come back to the participants of Phase III for final approval.

Annex

Name	Affiliation	e-mail address
Linda Thienpont	Chair WG-STFT	<a href="mailto:linda.thienpont@ugent.be">linda.thienpont@ugent.be</a>
Margherita Banci	Diasorin	<a href="mailto:margherita.banci@diasorin.it">margherita.banci@diasorin.it</a>
Graham Beastall	IFCC-BTA	<a href="mailto:gbeastall@googlemail.com">gbeastall@googlemail.com</a>
Ian Young	IFCC-SD	<a href="mailto:i.young@qub.ac.uk">i.young@qub.ac.uk</a>
Frank Quinn	Abbott	<a href="mailto:frank.quinn@abbott.com">frank.quinn@abbott.com</a>
Ralf Roeddiger	Roche Diagnostica	<a href="mailto:ralf.roeddiger@roche.com">ralf.roeddiger@roche.com</a>
Greg Miller	Virginia Commonwealth University	<a href="mailto:gmiller@vch.edu">gmiller@vch.edu</a>
Alberto Gutierrez	FDA	<a href="mailto:alberto.gutierrez@fda.hhs.gov">alberto.gutierrez@fda.hhs.gov</a>
Violeta Raneva	Laboratory of ReCCS, Japan	<a href="mailto:v-raneva@reccs.net">v-raneva@reccs.net</a>
Jerald C. Nelson	Loma Linda University	<a href="mailto:icnelson@llu.edu">icnelson@llu.edu</a>
Lothar Siekmann	IFCC-SD	<a href="mailto:lothar.siekmann@ukb.uni-bonn.de">lothar.siekmann@ukb.uni-bonn.de</a>
Anja Kessler	Reference Institute of Bioanalytics, DGKL	<a href="mailto:akessler@uni-bonn.de">akessler@uni-bonn.de</a>
Sherry Faye	Beckman Coulter	<a href="mailto:safaye@beckman.com">safaye@beckman.com</a>
Yung Chan	FDA	<a href="mailto:yung.chan@fda.hhs.gov">yung.chan@fda.hhs.gov</a>
Koki Arioka	Siemens Medical Diagnostics	<a href="mailto:koki.arioka@siemens.com">koki.arioka@siemens.com</a>
Offie Soldin	Georgetown University	<a href="mailto:os35@georgetown.edu">os35@georgetown.edu</a>
Carole Spencer	University Southern California	<a href="mailto:cspencer@usc.edu">cspencer@usc.edu</a>
Tom Wright	University Southern California	<a href="mailto:twright@usc.edu">twright@usc.edu</a>
Tamio Ieiri	International Univ. Shioya Hospital	<a href="mailto:ieiri-t@iuha.ac.jp">ieiri-t@iuha.ac.jp</a>
Courtney Harper	FDA	<a href="mailto:courtney.harper@fda.hhs.gov">courtney.harper@fda.hhs.gov</a>
Masanobu Kasai	Tosoh	<a href="mailto:masanobu-kasai-vn@tosoh.co.jp">masanobu-kasai-vn@tosoh.co.jp</a>
Masuo Inoue	Tosoh Corporation	<a href="mailto:masuo-inoue-hs@tosoh.co.jp">masuo-inoue-hs@tosoh.co.jp</a>
Judy Ogden	Tosoh Bioscience	<a href="mailto:judy.ogden@tosoh.com">judy.ogden@tosoh.com</a>
Hedwig Stepman	University of Ghent	<a href="mailto:hedwig.stepman@ugent.be">hedwig.stepman@ugent.be</a>

**Minutes made by:**

**Prof. Dr. Linda THIENPONT, Chair of the IFCC WG-STFT**

**Laboratory for Analytical Chemistry, Faculty of Pharmaceutical Sciences, UGent**

**Harelbekestraat 72, B-9000 GENT, Belgium**

**Tel. +32 9 264 81 04**

**e-mail: [linda.thienpont@ugent.be](mailto:linda.thienpont@ugent.be)**

## IFCC Working Group on Standardization of Thyroid Function Tests

### Annual meeting in conjunction with the AACC 2010 Conference

Anaheim Marriott  
Grand Ballroom – Salon D  
July 26th, 2010  
2:00 – 5:00 pm

Linda Thienpont  
Linda.thienpont@ugent.be



UNIVERSITEIT  
GENT

IFCC  
International Federation  
of Clinical Chemistry  
and Laboratory Medicine

## Introduction

### Agenda

- Welcome and roll call
- Status report
- Phase III of project
- Presentation by Prof. I. Young, IFCC SD Vice-Chair
- Discussion of future
- Other business?
- Closure of meeting

2

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Phase II (proof-of-concept) finalized



IFCC WG for Standardization of Thyroid Function Tests (WG-STFT)  
Chair: Prof. Dr. Linda Thienpont

Report update  
Proof-of-concept study

12 September 2009

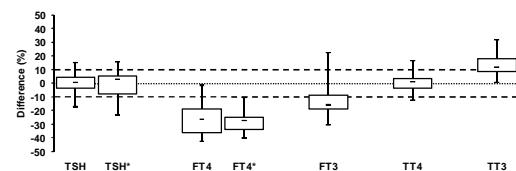
3

Linda M Thienpont - WG STFT - Anaheim - AACC 2010

IFCC  
International Federation  
of Clinical Chemistry  
and Laboratory Medicine

## Status report

### Phase II (proof-of-concept): before recalibration



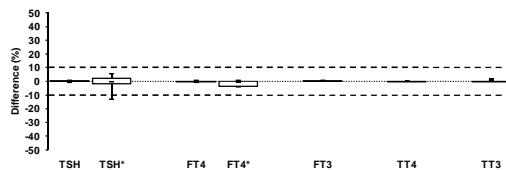
4

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Phase II (proof-of-concept): after recalibration



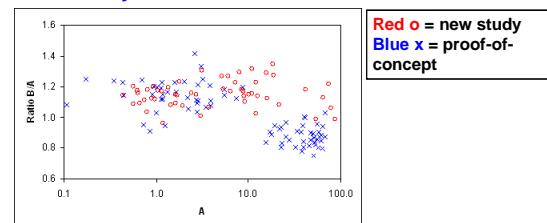
5

Linda M Thienpont - WG STFT - Anaheim - AACC 2010

IFCC  
International Federation  
of Clinical Chemistry  
and Laboratory Medicine

## Status report

Phase II (proof-of-concept): TSH clinical samples TSH ( $>10 \text{ mIU/L}$ ) ( $n = 30$ ) in comparison with euthyroid samples ( $n = 30$ ), all obtained from one hospital and analyzed in the same run in 2 replicates, & at random with 2 assays



6

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Publications

**Clinical Chemistry 2010; 56: 902-29**

Accompanied by Editorial (George Klee) and podcast

Report of the IFCC Working Group for

Standardization of Thyroid Function Tests;

Part 1: Thyroid-Stimulating Hormone

Part 2: Free Thyroxine and Free Triiodothyronine

Part 3: Total Thyroxine and Total Triiodothyronine



→ Huge interest: from readership (reprints); IVD manufacturers receive requests from customers to disclose their code(s); responsables for clinical and epidemiological studies ask information

7

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Forthcoming publications

**Clinical Chemistry and Laboratory Medicine 2010 (special issue dedicated to IFCC projects)**

Working Group for Standardization of Thyroid Function Tests – Status report

Status: revision submitted

**Clinical Chemistry and Laboratory Medicine 2010**

IFCC Recommended International Conventional Reference Procedure for the Measurement of the Substance Concentration of Free T4 in serum

Status: in preparation for submission Oct. 2010

8

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Related publications

**Clinica Chimica Acta 2010;411:1348-53**

FT4 immunoassays may display a pattern during pregnancy similar to the equilibrium dialysis ID-LC/tandem MS candidate reference measurement procedure in spite of susceptibility towards binding protein alterations

Authors: Anckaert E et al.

**Clinica Chimica Acta 2010**

Traceability to a common standard for protein measurements by immunoassay for in-vitro diagnostic purposes

Status: under revision

9

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Involvement of clinicians

Jan. 2010 – Call to clinicians for:

- Interest in joining the WG activities/discussions
- Help with procurement of clinical samples/repository panels

Several positive replies from Europe, Japan and the USA

- Restricted, however, to interest in joining the WG activities
- Up to now, procurement of clinical samples hampered because of the need for approval by local ethical committees
- Route not further pursued, but commercial source (see Phase III)

10

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Involvement of clinicians

Positive replies from:

- P. Abraham (Aberdeen Royal Infirmary, UK)
- M. Vanderpump (The Royal Free Hospital, London, UK)
- G.R. Williams (Imperial College London, Hammersmith Hospital, UK)
- F. Gasser (Hôpital Universitaire de Strasbourg, France)
- A. Cherrie (Centre Hospitalier Lyon Sud, France)
- P. Beck-Peccoz (University of Milan, IT)
- K. Ichihara (Yamaguchi Univ. Graduate School of Medicine, Ube, Japan)
- P. Ladenson (J. Hopkins Bloomberg School of Public Health, Baltimore, MD, USA)
- W. Meikle (ARUP, Salt Lake City, UT, USA)
- G. Miller (Virginia Commonwealth Univ., Richmond, VA, USA)
- J. Morris (Mayo Clinic, Rochester, MN, USA)

11

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



## Status report

### Contacts with other societies

The Endocrine Society (>W. Rosner)

### Further dissemination of results

- Nader Rifai (Editor of Clin Chem) offered assistance
- Need for a publication group of 3 to 4 authors ("on behalf of the WG-STFT")?

### Other suggestions?

12

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



**Status report – Related matters**

**C Ronin**  
**Siamed'Xpress**



**Contract Research Organization:**  
**Industrial research for new TSH testing for early diagnosis of hypothyroidism**  
**Validation of a clinical setting for early thyroid hormone treatment**  
**(will be funded by the French National Research Agency)**

13 Linda M Thienpont - WG STFT - Anaheim - AACC 2010 

**Phase III of project**

**Objective**  
**Studies for FT4 and TSH with clinically relevant sample populations (hypo-, eu-, hyperthyroid status)**

14 Linda M Thienpont - WG STFT - Anaheim - AACC 2010 

**Phase III of project**

**Objective**  
**Is assay performance on clinical samples identical to the performance on samples from 'apparently healthy' subjects?**

- FT4: relationship to the reference measurement procedure
- TSH: relationship to the 'all-procedure trimmed mean'

→ If yes, standardization possible

**Extend calibration to the full measurement range**

15 Linda M Thienpont - WG STFT - Anaheim - AACC 2010 

**Phase III of project**

**Source for samples**  
**PROMEDDX**  


Contact person: Dr. Jim Boushell  
Address: 10 Commerce Way, Norton, MA 02766, USA

16 Linda M Thienpont - WG STFT - Anaheim - AACC 2010 

**Phase III of project – Offer**

Sample Type:	Description
Matrix:	Endocrine Disease Subjects FT4
Supporting Data:	<ul style="list-style-type: none"> <li>Demographics (Age / Gender / Ethnicity)</li> <li><b>Free T4</b> concentration within corresponding medical diagnosis of:           <ul style="list-style-type: none"> <li>Euthyroid</li> <li>Hyperthyroid</li> <li>Hypothyroid</li> </ul> </li> <li>Current Medications &amp; Treatment</li> </ul>
Inclusion Criteria:	<ol style="list-style-type: none"> <li>Informed Consent Obtained</li> <li>Free T4 concentration within the suggested reference range corresponding to a diagnosis of:           <ol style="list-style-type: none"> <li>Euthyroid: 0.8 - 1.7 ng/dL</li> <li>Hyperthyroid: &gt; 1.7 ng/dL</li> <li>Hypothyroid: &lt; 0.8 ng/dL</li> </ol> </li> </ol>
Exclusion Criteria	<ol style="list-style-type: none"> <li>No Informed Consent</li> <li>Current T4 or recombinant TSH therapy</li> <li>Current diagnosis of any of the listed severe thyroidal conditions:           <ol style="list-style-type: none"> <li>Chronic Renal Failure</li> <li>Liver Cirrhosis</li> <li>Advanced (active) malignancy</li> <li>Sepsis</li> <li>Trauma</li> <li>Prolonged Fasting or Starvation</li> <li>Heart Failure</li> <li>Myocardial Infarction</li> </ol> </li> </ol>

17 Linda M Thienpont - WG STFT - Anaheim - AACC 2010 

**Phase III of project – Offer**

Sample Type:	Description
Matrix:	Endocrine Disease Subjects TSH
Supporting Data:	<ul style="list-style-type: none"> <li>Demographics (Age / Gender / Ethnicity)</li> <li><b>TSH</b> concentration within corresponding medical diagnosis of:           <ul style="list-style-type: none"> <li>Euthyroid</li> <li>Hyperthyroid</li> <li>Hypothyroid</li> </ul> </li> <li>Current Medications &amp; Treatment</li> </ul>
Inclusion Criteria:	<ol style="list-style-type: none"> <li>Informed Consent Obtained</li> <li>TSH concentration within the suggested reference range corresponding to a diagnosis of:           <ol style="list-style-type: none"> <li>Euthyroid: 0.3 - 3.0 uIU/mL</li> <li>Hyperthyroid: &lt; 0.3 uIU/mL</li> <li>Hypothyroid: &gt; 3.0 uIU/mL</li> </ol> </li> </ol>
Exclusion Criteria	<ol style="list-style-type: none"> <li>No Informed Consent</li> <li>Current T4 or recombinant TSH therapy</li> <li>Current diagnosis of any of the listed severe thyroidal conditions:           <ol style="list-style-type: none"> <li>Chronic Renal Failure</li> <li>Liver Cirrhosis</li> <li>Advanced (active) malignancy</li> <li>Sepsis</li> <li>Trauma</li> <li>Prolonged Fasting or Starvation</li> <li>Heart Failure</li> <li>Myocardial Infarction</li> </ol> </li> </ol>

18 Linda M Thienpont - WG STFT - Anaheim - AACC 2010 

### Phase III of project – Offer

Description	
Temp. Storage	≤20°C
Processing	Serum: 30 x 0.5 ml
Quantity	<p>FT4: 90 Subjects: • 30 Euthyroid • 30 Hyperthyroid • 30 Hypothyroid</p> <p>TSH: 100 Subjects: • 30 Euthyroid • 30 Hyperthyroid • 40 Hypothyroid</p>
Extended Price	\$ 450 per subject
Targeted Delivery	10-15 weeks from initiation

19

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



### Phase III of project – Offer

#### Amendments requested

*Storage temperature: minus 70°C*

*Categories qualifying the hypo-, eu-, and hyperthyroidism:* in each interval we need samples with concentrations that cover the entire range as specified, e.g. for TSH, between the ULRI and  $\pm$  70 mIU/L (hypo) or between 0.01 mIU/L and the LLRI (more or less at equidistance)

*Clinical information on donors:* clinical diagnosis and co-morbidities required

*Blood collection procedure:* more details required, such as type of blood tube, clotting time, temperature, handling temperature, total elapsed time from collection to aliquot freezing.

*Different centers or only 1 center?*

20

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



### Phase III of project – Offer

#### Amendments requested – Reply

*Storage temperature: Minus 70°C*

*Categories qualifying the hypo-, eu-, and hyperthyroidism:* PromedDX people will do their best to provide a clear distribution, without significant concentration in any one range, however, to predict/promise this initially would be callous on our part (it is very difficult to identify and enroll patients that are not on any type of treatment for their thyroid disease....)

*Clinical information on donors:* clinical diagnosis and co-morbidities required

*Blood collection procedure:* PromedDX will provide a clear handling instruction from blood draw, to final aliquotting and long term storage

*Different centers or only 1 center?* Due to the requirement of 'not thyroid treatment', PromedDX must have multiple sites participating in order to achieve the enrollment numbers (and with good fortune, the enrollment rate)

21

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



### Phase III of project

#### Some further technical aspects

*Volume per sample:* 15 mL aliquoted per 0.5 mL

*Required volume for FT4 analysis by ED ID-MS:* 3 mL

*Remaining volume:* 12 mL

*Available volume per manufacturer:* at least 2 aliquots (8 manufacturers); each MF decides on the assays to include; remaining volume to purchase

*Positive reply for participation:* 7 (however, with request for flexibility in invoicing), 1 decision pending

*Timelines:* if we place the order in August, November 2010

*Measurement protocol to decide*

22

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



### Phase III of project

#### Comment and proposal by Roche (>M. Rottmann)

Because of FDA requirement that a panel for standardization should cover 80% of the measurement range of an assay and the presumption that it will be extremely difficult to obtain very high FT4 concentrations, add 3 "spiked" samples to concentration levels of 30, 60 and 90 pmol/L

Include them in the clinical study

Verify whether such samples are commutable with the different assays

If yes, facilitates to obtain the high end of the measurement range

Roche is prepared to make the samples

23

Linda M Thienpont - WG STFT - Anaheim - AACC 2010



### Discussion of the future of the project

*Transformation of WG-STFT into Committee*

*Involvement of a broader forum for implementation of standardization (call to all stakeholders to actively participate in the effort to standardization)*

*Others items?*

*Concerns by IVD industry:*

Will standardization to 'all procedure trimmed mean' be accepted by FDA? What about the traceability to the WHO?

*FDA point-of-view?*

*Go/No go decision after phase III?*

24

Linda M Thienpont - WG STFT - Anaheim - AACC 2010





## IFCC SD presentation

Presentation by Prof. I. Young, IFCC SD Vice-Chair

25

Linda M Thienpont - WG STFT - Anaheim - AACC 2010

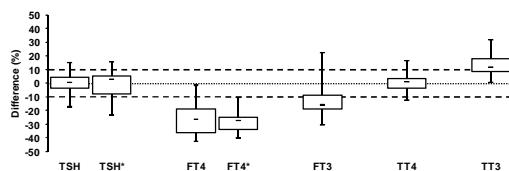


## Standardization of Thyroid Function Tests

- Importance of distinguishing between Standardization vs. Harmonization
- Either option may be followed
- Maintain clarity about which approach is to be followed, and actively weigh up advantages and disadvantages of each before proceeding

## Standardization of Thyroid Function Tests

- **FT4**  
"All assays measured lower than the RMP"  
"For the majority of assays the impact of standardization would be considerable"
- **FT3**  
"The standardization status was similar to that for FT4: almost all assays were negatively biased in comparison to the RMP, apart from one."
- **TT3**  
"All assays were positively biased, some to a minor extent (see the LL of +1%), others to an extreme extent (see the UL of +32%). This indicates that apart from a minority of assays, most assays would see a significant decrease in their TT3 values after standardization. "



## Standardization of Thyroid Function Tests

- Standardization will have considerable impact on results, reference intervals and decision limits
- Essential to ensure that there is understanding of this from manufacturers, laboratories, regulators, clinicians and patient groups