The Committee for Standardization of Thyroid Function Tests (C-STFT) of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

IFCC 2018 General Conference Notes

Closed meeting - 11/09/18 (9:00 AM-11:00 AM)

List of participants

Hubert Vesper, Akira Hishinuma, Katleen Van Uytfanghe, Michael Rottmann, Valentina Vidranski Jasbinder Kaur, Gordon Avery, Radek Kucera (representing Anette Adelmann), Candice Ulmer

1 Roll call and Introduction of new committee members

Update on the current committee members and corresponding members nominated by National Societies. An overview can be found at http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/.

2 New terms of reference

The terms of reference, see http://www.ifcc.org/ifcc-scientific-division/sd-committees/c-stft/, have changed. The focus is now on implementation and sustainability.

3 Approval minutes of the meeting at the AACC 2018

The minutes were unanimously approved.

4 Present and Future Progress

4.1 The reference laboratory network

4.1.1 Summary of Past Decisions/Objectives

- The reference laboratory network was established in order to ensure consistent accuracy and traceability over time, and to increase RMP laboratory capacity for manufacturers and laboratories. All laboratories were asked to implement the IFCC endorsed FT4 RMP, described in Clin Chem Lab Med 2007;45:934-6 and Clin Chem Lab Med 2011;49:1275-81.
- The network decided to assess current agreement among candidate RMP laboratories, align measurement results as needed, and use the network to establish target values based on all-laboratory means.
- Reference laboratory network Candidates: Ref4U (Belgium), CDC (USA), Radboud University Medical Center of Nijmegen (The Netherlands), Reference Material Institute for Clinical Chemistry Standards (Japan)
- The IFCC endorsed FT4 RMP uses ED with ID-LC/MS/MS and has specific conditions for the ED process. The CRM used is IRMM 468 for calibration traceability.
- The suggested analytical performance requirements for reference measurement procedures are:
  Imprecision: ≤5%,
  Bias: ±2.5%,

Expanded measurement uncertainty: 7.6%,
LoD/LoQ: 0.5/1.3 pmol/L (0.04/0.10 ng/dL)

4.1.2 Current Progress/first network method comparison

- The objectives for this initial method comparison were threefold:
  (i) assess agreement among laboratories,
  (ii) identify potential sources of bias, and
  (iii) review and refine RMP SOP as needed
- For the experimental design the network decided to use 20 blinded euthyroid, single-donor samples and measure them on 3-4 independent occasions. This should rule out any influence of possible protein leakage on the assessment of bias, and gives us the possibility to study intra-laboratory variation.
- Preliminary results:
  - The correlation of the 4 lab results to the overall mean is very good, demonstrating that the RMP SOP can be reproduced in different labs.
  - The mean bias of labs are within +-2.5% bias, but there is room for improvement. Labs show consistent bias across the concentration range, and this indicates calibration differences rather than sample related issues.

4.1.3 Future efforts

The reference laboratory network members will

- Improve the calibration status of network laboratories.
  The CDC will prepare calibrators for common use. The calibrators will be aliquoted in ampules. The concentration will be verified using Q NMR in order to have an independent assessment of the concentration. We aim at the end of the year to ship the ampules to the different laboratories. Our purpose is to get the systematic bias between the candidate reference laboratories to less than 2%.
- Refine RMP SOP based on feedback from network members to facilitate setup and implementation of the RMP in other labs.
- After these tasks are completed, a new method comparison will be performed. This new study will include samples in the hypo- and hyperthyroid concentration range. This new study is planned to be completed by 3rd or 4th quarter of 2019.
- Define protocol for maintaining the network and for enrolling new candidate members. A first draft of the protocol is planned to be developed for review first half of 2019.

The network will serve as a point of reference, each network laboratory will serve as reference laboratory for his/her region.

4.2 Survey on the impact of standardization/harmonization for laboratories and assay manufacturers

- We will compile professor Thienponts survey on the impact of standardization/harmonization for laboratories and assay manufacturers.
- One of the first conclusions is that professional organizations see no problems with implementing standardized/harmonized assays.
- The compilation will be made available to relevant stakeholders.

4.3 Reference ranges

- Based on the input we received regional reference ranges need to be established.

- The TSH reference range project in Japan is ongoing. Samples will likely be distributed before summer next year (for details, see the appendix). There is interest from other regions (Croatia and India) to set-up similar projects.
- We will work on a guidance document to help with linking these reference range studies to the IFCC reference system. This should include information on what kind of population to test and how to calibrate the assays. A draft of the guidance document is planned to be completed by end of 2019.
- The committee will reach out to NHANES and the EUthyroid-project to assess if these studies and data sources can be used for developing reference ranges.
- The committee agreed that is will be important to have separate reference ranges in children and pregnant women. Potential analytical challenges with measuring thyroid hormones in pregnant women were discussed. These challenges can be addressed once the network is established and operational.
- The use of common reference ranges by manufacturers and related regulatory challenges were discussed. The committee agreed that common reference ranges should be used whenever possible. The committee members will collect more information to better describe the challenges in the EU and US.

4.4 TSH 3rd follow-up panel

- New samples need to be collected. We will send out a questionnaire in the first quarter of 2019 seeking for
    - (more) collection sites
    - support from industry
- We will collect more samples in order to have panels for calibration and for verifying calibration for those doing reference interval studies.
- The targets will be set by the same 4 laboratories as for the previous panels.

4.5 Education

- To update our website, we seek input from all stakeholders. A call for suggested edits will be send out first quarter of 2019. Especially the tabs “patients” and “clinicians” can be more educative.
  It was suggested to translate the existing information into other languages in order to more easily disseminate information about our work. Once the websites are revised, we will approach individuals from certain regions to help with translation.
- The committee will revise slides for members to be used at meetings and conferences.
- The committee will provide more education to physicians and other healthcare providers about the importance of standardized thyroid function tests. One suggested approach was attending meetings and giving presentations to thyroid meetings. Committee members were encouraged to identify meetings in their region.

5 Next meetings

We plan to have a C-STFT meeting in conjunction with

- the next EuroMedLab Congress to be held in Barcelona from 19 to 23 May 2019.
  Our C-STFT meeting is scheduled on May 20th. More details will follow.
- The next Annual AACC meeting to be held in Anaheim, California from 4 to 8 August 2019.

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Open meeting - 11/09/18 (13:00 PM-14:00 PM)

List of participants

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6 Summary of closed meeting

Dr. Vesper gave a summary of the closed meeting, see minutes above.

This was followed by a short discussion in which following suggestions/comments were made

- The committee should approach MedTech in order to work with them and get a more clear view on the guidelines that will be written based on the new European regulation. Gordon Avery will help with establishing contact.
- Concerns have been raised by manufacturers about the use of common reference ranges. The committee will collect more information to help manufactures overcoming this challenge. The committee chair pointed out that common reference ranges have successfully be implemented for testosterone.
- It was suggested to make the work of the IFCC committee more known in the Asia/Pacific region. The chair will work with members and stakeholders to identify meetings and other events.
- A question was raised on the FDA's point of view of accepting reference measurement procedures rather than requiring a comparison to the predicate. Based on comments made by FDA at the AACC meeting in August 2018, appropriate comparisons to reference methods with be taken into consideration in submissions.

Appendix – Japanese Reference Interval study.

In Japan, a harmonization project is currently on-going. Our TSH harmonization project was presented to the government officials in the Ministry of Health, Labour and Welfare on behalf of four scientific societies, Japan Thyroid Association, Japan Society of Clinical Chemistry, Japanese Society of Laboratory Medicine, and Japanese Committee for Clinical Laboratory Standards, the government officials contacted Japan Association of Clinical Reagents Industries (JACRI) in order to explore the practical issues to discuss the IVD companies. The government agreed that IVD companies present conversion factors when they do not change the reagent systems. JACRI expressed concerns about the reference intervals reported in Clinical Chemistry because the study was performed in the Caucasian population. Therefore, a project to develop Japanese RI is running. In this project, 10 different manufacturers, which sell their products to the Japanese market will participate. The samples (120) to establish the RI are currently collected and will be measured under the same conditions as the samples for the RI which the C-STFT published in Clin. Chem, i.e. with the technically harmonized TSH-assays.