Letter to the Editor

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Standardization of Free T_4 and Harmonization of TSH Measurements: A Request for Input from Endocrinologists and Other Physicians

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Dear Editor,

Given the prevalence of thyroid disorders and the subtle signs and symptoms which may accompany subclinical disease, reliable laboratory testing for serum TSH and free thyroid hormones is important for both primary care physicians and endocrinologists. The laboratory community has recognized the need for standardization of thyroid function tests to achieve comparability of measurement results between methods. This applies particularly for free T_4 tests, which may be considered controversial in terms of clinical and analytical validity. But there is also variability in TSH testing – a fact which has not been emphasized in ongoing discussions regarding lowering of the upper limit of normal and/or common decision limits to start treatment for hypothyroidism.

In response to this need, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) formed the Working Group for Standardization of Thyroid Function Tests (WG-STFT) in 2005. Today the WG is a full Committee (C-STFT) and we authors are respectively chair, member and past president at IFCC. We have worked over the years towards the goal of standardization of free T_4 and TSH testing. Because, unlike free T_4, there is no reference measurement procedure for TSH, we have proposed an alternative to standardization for this test called harmonization [1–4]. We performed different phases of method comparison studies to investigate and confirm the technical feasibility of standardization of free T_4 and harmonization of TSH tests, but also with attention to fit-for-the-purpose analytical quality [5–7]. The uniform recalibration basis that will be achieved through the activities of the C-STFT will allow the participating assays to use common reference intervals or decision limits for interpretation of results. However, in view of the Committee's approach to standardization/harmonization with clinically relevant patient samples, this recalibration basis will uniquely be valid for a patient population of which the used samples form a representative selection (in essence apparently euthyroid individuals, and uncomplicated hypo- or hyperthyroid patients) [7].

For free T_4, the variability is substantial. Standardization will change results significantly – perhaps as much as 80% at the upper limit of the normal range – for some assays. For TSH the alterations introduced by harmonization will be milder (approx. 20%). The Committee, comprising laboratory professionals and manufacturers, got a positive response to the technical approach from the Food and Drug Administration (FDA). They recognized that in spite of the limitation of the approach of not applying to all clinical situations, it was inevitably an important step towards better understanding more subtle assay difference in other populations. Therefore, they agreed with the C-STFT's next plan to establish a dialogue basis with an as broad spectrum of stakeholders as possible, and investigate with them the risks associated with implementing the current standardization/harmonization step, and/or how to proceed.

To this end, we are reaching out here to the clinical stakeholders to seek views on the benefits and risks arising from free T_4 standardization and TSH harmonization.

1 *Benefits.* We wish to learn of the benefits that you endocrinologists and other physicians think would be achieved if all free T_4 and TSH assays gave comparable results for the aforementioned relevant categories of patients.
2 *Risks.* We wish to learn of the risks to patient safety and clinical outcomes that you think may arise as a consequence of a change in the numerical results for patients with thyroid disorders who are being followed, despite the appropriate similar change in the refer-

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ence intervals. We ask to pay particular attention to the question whether standardization/harmonization restricted to diagnosis/monitoring of uncomplicated hypo- and hyperthyroidism may detract from assay differences for important other clinical populations (nonthyroidal illness, pregnancy, elderly people).

3 *Implementation.* We wish to hear your views on how clinical laboratories can minimize the identified risks from free T_4 standardization and TSH harmonization, and on the role that you could play yourself in your contact with the patients you treat.

This call is being launched in parallel to several clinical journals and to professional organizations for doctors and laboratory specialists.

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Disclosure Statement

Nothing to declare.

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