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Standardization of Free Thyroxine and Harmonization of Thyrotropin 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 that may accompany subclinical disease, reliable laboratory testing for serum thyrotropin (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 thyroxine (fT4) tests, which may be considered controversial in terms of clinical and analytical validity. However, there is also variability in TSH testing—a fact that has not been emphasized in ongoing discussions regarding lowering 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 a Working Group for Standardization of Thyroid Function Tests (WG-STFT) in 2005. Today, the working group is a full Committee (C-STFT), and we authors are respectively chair, member, and past president at the IFCC. We have worked over the years toward the goal of standardization of fT4 and TSH testing. Because, unlike fT4, there is no reference measurement procedure for TSH, we have proposed an alternative to standardization for this test called harmonization (1,2). Different phases of method comparison studies were performed to investigate and confirm the feasibility of standardization of fT4 and harmonization of TSH tests, but also with attention to fit-for-purpose analytical quality (3,4).

For fT4, 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 (approximately 20%). The Committee, comprising laboratory professionals and manufacturers, has received a positive response for this approach from the Food and Drug Administration (FDA), albeit with the caveat to investigate the risks associated with changes in the numerical results for some of the assays.

To this end, we are reaching out to stakeholders to seek views on the benefits and risks arising from fT4 standardization and TSH harmonization.

1. *Benefits*: We wish to learn about the benefits that you think would be achieved if all fT4 and TSH assays gave comparable results on patient samples.
2. *Risks*: We wish to learn about 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 appropriate adjustments of the reference intervals. Particular attention should be paid to the question of whether standardization for uncomplicated hypo- and hyperthyroidism may detract from assay differences for important clinical populations (nonthyroidal illness, and elderly and pregnant individuals).
3. *Implementation*: We wish to hear your views on how clinical laboratories can minimize the identified risks from fT4 standardization and TSH harmonization, and about the role that you could play for the patients you treat.

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

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