Interlaboratory Comparison of Thyroglobulin Measurements for Patients with Recurrent or Metastatic Differentiated Thyroid Cancer

To the Editor:

Serum thyroglobulin (Tg) is a tumor marker for persistent and recurrent thyroid cancer (1). However, there are technical limitations of Tg measurements by both RIA and two-site immunometric assays, and Tg results vary among laboratories (1, 2). Some of the discrepancy is likely linked to Tg autoantibody (TgAb) interference as TgAb is detectable by RIA in 18–40% of patients with differentiated thyroid cancer (3, 4). Failure to use the same Tg standard, preferably International Standard CRM-457, is potentially another source of interlaboratory differences in results (5, 6).

In January 1999, we implemented a protocol by which we administer rhTSH (Thyrogen; Genzyme Transgenic Corporation) to patients with thyroid cancer. Serum Tg is measured before and 72 h after 2 days of rhTSH administration. University of Southern California (USC) Endocrine Services Section served as the central laboratory for the original Thyrogen protocol study sites from which the recommendations concerning the interpretation of rhTSH-stimulated Tg concentrations were derived (7). From January 1999 through July 2001, we split serum samples from these patients and sent them for Tg measurements to USC and to Endocrine Sciences/Esoterix, Inc., Endocrinology (Calabasas, CA), where we had sent samples from thyroid cancer patients before 1999. Measurements were not performed as part of a clinical research project and were subject to the usual day-to-day interassay variation. Patients were informed that their blood was being sent to two laboratories and told the reason (to ensure comparability of results).

We studied 97 paired samples from 40 patients. All samples from any one patient were tested in a single assay run. All statistical analyses were performed using GB-Stat Ver. 7.0 statistical software (Dynamic Microsystems).

At USC, sera are screened for the presence of Tg antibodies (Tg Abs) by a quantitative RIA method with a detection limit of 1.0 IU/mL, which is calibrated against WHO First International Reference Preparation 65/93 (Kronus, San Clemente, CA) (7). For TgAb-negative samples, Tg was measured by an immunochromiluminometric assay (ICMA; Nichols Institutes Diagnostics). The detection limit was 0.5 µg/L. For TgAb-positive sera, Tg was measured by RIA, with a detection limit of 0.2 µg/L and a functional sensitivity of 0.5 µg/L. Both assays use CRM-457 as standard (4). For clinical samples, USC reports values <1 µg/L as such for both methods.

Esoterix used assays developed in house. They first screened all Tg samples for the presence of TgAb by a chemiluminescent immunoprecipitation assay with a detection limit of 1.0 IU/mL. Before June 29, 2000, all samples were measured by RIA with a functional sensitivity of 2 µg/L using an early Tg calibrator. Subsequently, they used the RIA for TgAb-positive samples, but TgAb-negative samples were measured in an ICMA with a functional sensitivity of 0.5 µg/L. As of June 29, both the ICMA and RIA were standardized against CRM-457. This change decreased the apparent functional sensitivity of the RIA to 3 µg/L.

TgAb was undetectable in 31 patients (80 samples) and present in 9 (17 samples). We obtained 42 specimens during the Thyrogen protocol (21 patients) and 38 specimens (20 patients) at other times. The regression analysis parameters were nearly identical for patients having Tg measured at days 1 and 5 of the Thyrogen protocol and for the Tg results during the Thyrogen test and those obtained while on thyroid hormone suppression alone or while hypothyroid with endogenously increased TSH. Thus we examined all values together.

In the TgAb-negative samples, the regression equation, uncorrected for changes in standards or methods, was: \( y \) (Esotrix) = 5.22 + 0.51x (USC) (\( r^2 = 0.75 \); SE slope, 0.047; SE intercept, 5.2, \( r = 0.999 \); Fig. 1). In the samples with TgAb, it was: \( y \) = 2.33 + 0.4x (\( r^2 = 0.80 \); SE slope, 0.047; SE constant, 0.75; \( r = 0.907 \)). To ensure that the undetectable values at both laboratories were not unfairly weighting our regression analysis, we evaluated the linear regression parameters for all Tg values, excluding TgAb-positive values (\( n = 80 \)) and all samples with measurable Tg (non-TgAb positive values (\( n = 52 \)). Values that were undetectable were considered to be halfway between zero and the number at the lower limit of detectability. The slopes of the two linear regression lines were identical.

Despite the similarity of technique used by the two laboratories, the Tg values, although well correlated, are not equivalent, with USC results 1.53 and 1.34 times higher than those from Esotrix for all TgAb-negative samples with measurable Tg concentrations, before and after the change to the CRM-457 standard by Esotrix on June 29, 2000. This 1.3- to 1.5-fold difference may reflect differences in

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Fig. 1. Linear regression of all TgAb-negative measurements (\( n = 80 \)).

\( y \) (Esotrix) = 5.22 + 0.51x (USC); \( r = 0.999 \).
Tg epitopes recognized by the assays.

In conclusion, USC Endocrine Services and Esoterix, Inc. provide highly correlated Tg results. The results from USC tend to be higher, especially at concentrations $>$5 μg/L, with both laboratories providing reliable measurements. Samples from the same patient should be followed with the same assay.

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References

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Correction
In the article entitled “Determination of Coumarin-type Anticoagulants in Human Plasma by HPLC–Electrospray Ionization Tandem Mass Spectrometry with an Ion Trap Detector” by M. Kollroser and C. Schober (Clin Chem 2002;48:84–91), the phrase “phenylpropyl ring” in line 2 of the second column on page 90 should read “phenyl ring”. In addition, the proposed product ion structures in Fig. 2 were incorrectly drawn. The correct structures are shown below. The authors thank Douwe de Boer for pointing out these errors.

Correct structures for Fig. 2.
Correct structure for panels A, B, and D is shown on the left; correct structure for panel C is shown on the right.