SIEMENS

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# Results of Sample Testing for the Determination of Reference Intervals in Apparently Healthy Pediatric Subjects for ADVIA Centaur® Systems, Dimension Vista® and Dimension EXL® Systems Thyroid Assays

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## Abstract

**Introduction:** Age-specific reference intervals are necessary for appropriate interpretation of thyroid hormone measurements in the pediatric population and may vary due to methodological differences. A challenge for establishing pediatric reference intervals has been the availability of well-characterized samples from healthy pediatric subjects. Of the few studies that provide this information, most are based on specimens from patients who were hospitalized or required medical care. This study used methodology consistent with CLSI guidelines to pedigree and collect samples from apparently healthy pediatric subjects presenting for regular well child care.

**Objective:** To test well-characterized specimens from healthy pediatric subjects to establish pediatric reference intervals for various assays and instruments.

**Methods:** Eight US sites prospectively collected samples from apparently healthy pediatric subjects, under institutionally approved consent/assent procedures. Subjects were normal according to CDC weight- and height-based growth charts, were free of chronic and acute diseases, were not on medication, had no family history of thyroid dysfunction, no visible or palpable goiters, and were negative for anti-thyroglobuin and anti-thyroid peroxidase antibodies. Three age subgroups were analyzed with approximately equal numbers of males and females. Samples were shipped to a central laboratory and tested in singleton using multiple Siemens immunoassay systems. The lower and upper reference limits were defined as the 2.5th and the 97.5th percentiles of the distribution of test results for each of the two older subgroups. For the infant subgroup, a robust method (Horn and Pesce) was used to calculate the reference intervals.

**Results:** Presented in the poster.

**Conclusion:** Pediatric reference intervals were established for ADVIA Centaur, Dimension Vista and Dimension EXL thyroid assays using rigorously pedigreed samples. These data will assist with the appropriate interpretation of thyroid measurements in infants, children and adolescents.

## Background

Establishing pediatric reference intervals has been challenged by the lack of availability of well characterized samples from the healthy pediatric population. Users of thyroid assays have clearly communicated that the availability of manufacturer pediatric intervals would be valuable information.

## Materials and Methods

### Three Age Subgroups

- Infants: subjects aged ≥1 month to <24 months of age
- Children: subjects aged ≥2 to <13 years of age
- Adolescent: subjects aged ≥13 to <21 years of age

A representative sample of age groups, gender, US geography and diversity was collected.

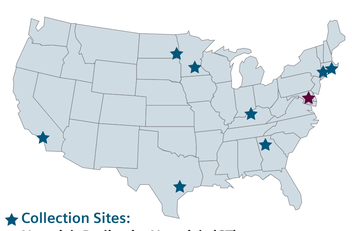
### Subject Inclusions Criteria

The following Inclusion criteria were used for the selection of the study subjects:

- Subject aged ≥1-month-old to <21 years of age
- No active chronic diseases, with the exception of allergic diseases
- No active acute disease
- No prescribed medications in the 7 days preceding sample collection
- No contraceptive medication in the 90 days preceding sample collection
- No over the counter medications in the 7 days preceding sample collection except vitamin and nutritional supplement
- Healthy weight indicated by a BMI or weight-for-length
- Length-for-age or stature-for-age between the 5th and 95th percentiles.
- No suspicion of premature or delayed puberty, based on physical examination
- Subject specimen negative for autoantibody against TPO and TG
- No pregnant female subject
- No risk factors for thyroid disorders

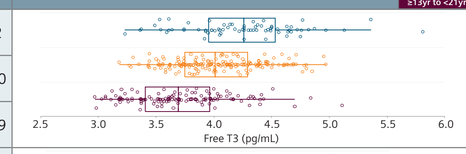
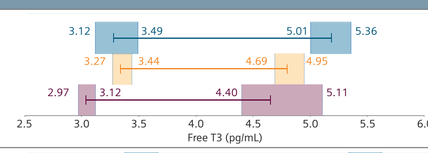
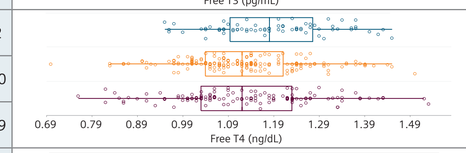
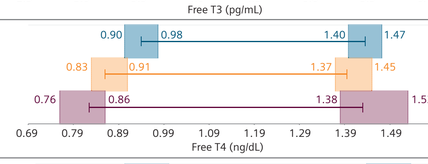
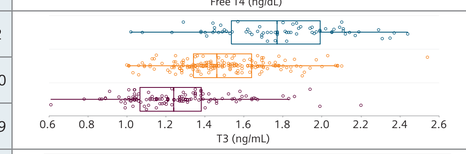
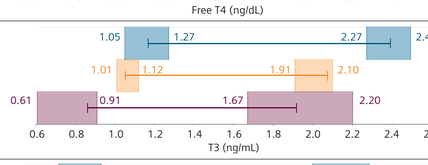
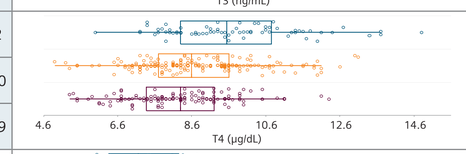
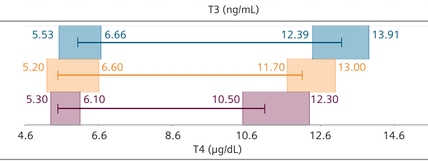
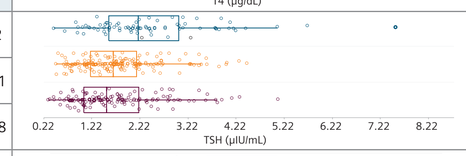
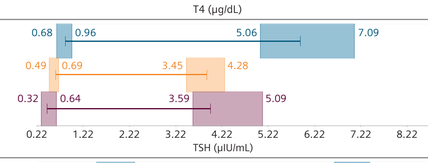
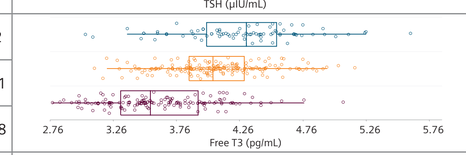
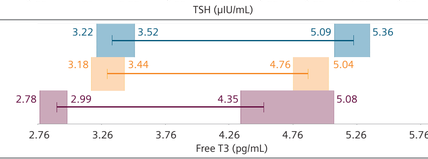
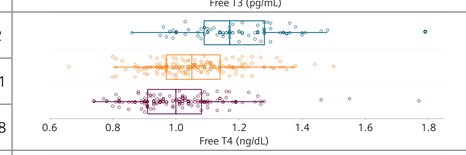
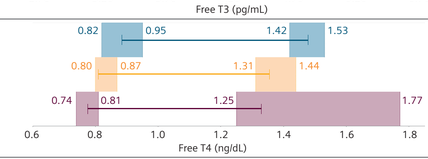
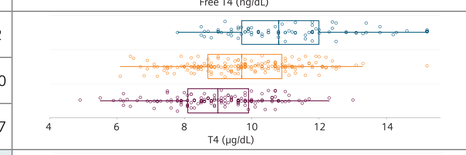
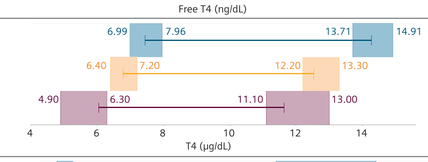
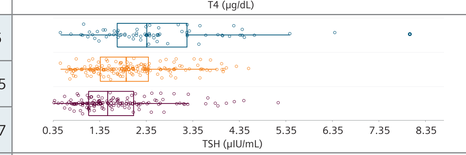
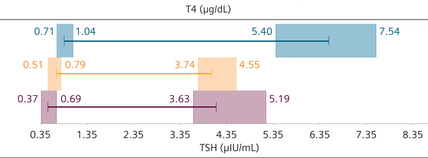
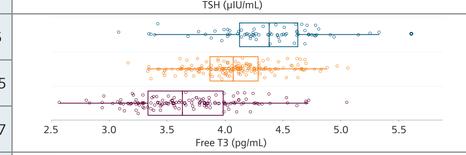
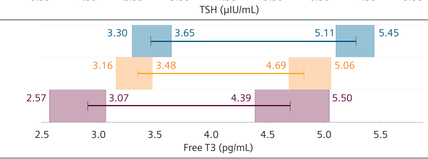
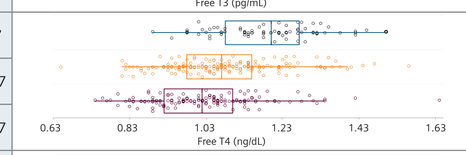
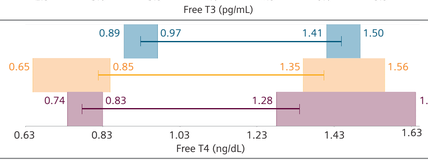
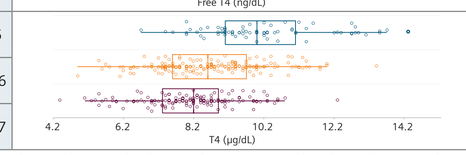
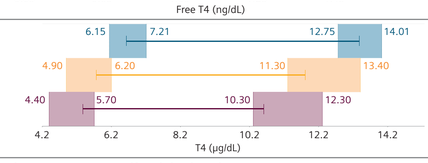
### Sample Testing

Eight sites across the US prospectively collected serum samples which were stored at -70°C and tested at a single laboratory in singleton on three Siemens systems: ADVIA Centaur, Dimension Vista, and Dimension EXL, from March 6th, 2012 up to June 20th, 2013.



★ **Collection Sites:**
**Norwich Pediatric, Norwich (CT)**
**Odyssey Research, Fargo (ND)**
**Omega Medical Research, Warwick (RI)**
**West Coast Clinical Trials, Costa Mesa (CA)**
**Kentucky Clinical Trials Laboratory, Louisville (KY)**
**Aspen Medical Research Foundation, Saint Paul (MN)**
**Pediatric Healthcare of Northwest Houston, Tomball (TX)**
**Pediatric and Adolescent Medicine, Marietta (GA)**
★ **Testing Site: Clinical Pathology Research Laboratory, University of Maryland School of Medicine, Baltimore (MD)**

## Results

| System | Assay[a] | n | Distribution of Test Results (Infant ≥1mo to <24mo; Children ≥2yr to <13yr; Adolescent ≥13yr to <21yr) | 90% Confidence Limits | 95% RI |
|---|---|---|---|---|---|
| ADVIA Centaur | FT3 | 72 |  |  | 3.28–5.19 pg/mL |
| | | 190 | | | 3.34–4.80 pg/mL |
| | | 129 | | | 3.04–4.65 pg/mL |
| | FT4 | 72 |  |  | 0.94–1.44 ng/dL |
| | | 190 | | | 0.86–1.40 ng/dL |
| | | 129 | | | 0.83–1.43 ng/dL |
| | T3 | 72 |  |  | 1.17–2.39 ng/mL |
| | | 190 | | | 1.05–2.07 ng/mL |
| | | 129 | | | 0.86–1.92 ng/mL |
| | T4 | 72 |  |  | 6.03–13.18 µg/dL |
| | | 190 | | | 5.50–12.10 µg/dL |
| | | 129 | | | 5.50–11.10 µg/dL |
| Dimension VISTA* | TSH | 82 |  |  | 0.816–5.91 µIU/mL |
| | | 191 | | | 0.662–3.90 µIU/mL |
| | | 148 | | | 0.438–3.98 µIU/mL |
| | FT3 | 82 |  |  | 3.34–5.24 pg/mL |
| | | 191 | | | 3.31–4.88 pg/mL |
| | | 148 | | | 2.91–4.53 pg/mL |
| | FT4 | 82 |  |  | 0.88–1.48 ng/dL |
| | | 191 | | | 0.81–1.35 ng/dL |
| | | 148 | | | 0.78–1.33 ng/dL |
| | T4 | 82 |  |  | 7.4–14.3 µg/dL |
| | | 190 | | | 6.8–12.5 µg/dL |
| | | 147 | | | 6.0–11.6 µg/dL |
| Dimension EXL* | TSH | 75 |  |  | 0.867–6.43 µIU/mL |
| | | 185 | | | 0.704–4.01 µIU/mL |
| | | 147 | | | 0.516–4.13 µIU/mL |
| | FT3 | 75 |  |  | 3.47–5.29 pg/mL |
| | | 185 | | | 3.35–4.82 pg/mL |
| | | 147 | | | 2.91–4.70 pg/mL |
| | FT4 | 77 |  |  | 0.93–1.45 ng/dL |
| | | 187 | | | 0.82–1.40 ng/dL |
| | | 147 | | | 0.78–1.34 ng/dL |
| | T4 | 75 |  |  | 6.6–13.4 µg/dL |
| | | 186 | | | 5.8–11.8 µg/dL |
| | | 147 | | | 5.4–10.6 µg/dL |

*The Dimension Vista and Dimension EXL pediatric reference intervals are not applicable in the U.S.

## Statistical Method

The robust method was used to analyze the smallest group, infants. A log transformation was used for the TSH infant data, highly positively skewed; a robust symmetrical method was used to establish reference intervals for the transformed TSH data, and for all other analytes, namely, FT3, FT4, T3 and T4, all with normal distributions.

The CLSI guideline[1] recommends the robust method, which uses a resampling, or bootstrap, approach that does not assume an underlying Gaussian distribution. The robust estimator has the best performance for small sample sizes[2], especially the upper reference interval values, which are consistently less affected by outliers. Using the performance measure root mean square error (RMSE), the robust method produced lower RMSE, thus tighter confidence intervals and medically more conservative reference intervals, when compared with other methods.

The reference intervals among all three age groups were consistent with our knowledge of physiology that TSH declines with age.

## Conclusion

Pediatric reference intervals were established for 12 Siemens thyroid assays. For each assay, reference intervals were established for the sub-populations for infants, children and adolescents. All reference interval boundaries are within their specific assay measuring ranges.

**References**

1. CLSI, "Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline---Third Edition", Volume 28, Number 30, Guideline C28-A3c, 2010.
2. Horn PS, Pesce AJ, Copeland BE. A robust approach to reference interval estimation and evaluation. Clin Chem 1998;44:622-631.

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