AMERICAN THYROID ASSOCIATION®

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Standardization and Harmonization

ABOUT

The Laboratory Services Committee of the American Thyroid Association® (ATA) conducted a survey of ATA® members to identify areas of member interest for education in pathology and laboratory medicine. In response to the results of the survey, the Lab Service Committee developed a series of educational materials to share with the ATA® membership. The topics below were ranked as high educational priorities amongst the membership.

OVERVIEW

Analyte reference intervals for healthy subjects define the benchmarks for laboratory test values, which in turn allow clinicians to determine a diagnosis, establish progression of disease, and monitor response to therapy. Since test conditions and methods vary from laboratory to laboratory and even within a laboratory over time depending on the instrument, method and reagents used, laboratories are required to verify reference intervals regularly. Despite this quality assurance process, there are significant inter-laboratory differences at any given time and intra-laboratory differences over time that limit the application of clinical practice guidelines and create challenges for patients and treating clinicians.

Variability of laboratory testing is prevalent in all aspects of thyroidology including biochemistry, cytology, histopathology, immunohistochemistry and molecular diagnostics. This document will address only the biochemical testing that is used for patients with thyroid disorders.

Laboratory testing for patients with thyroid diseases includes many biochemical analyses. The highest volume and therefore highest impact testing involves thyroxine (T4), triiodothyronine (T3) and thyrotropin (thyroid stimulating hormone, TSH), which have been the subject of several studies and multiple initiatives that will be reviewed. Other areas of concern include thyroglobulin (TG), antibodies to thyroid antigens including TG, thyroid peroxidase (TPO) and others, as well as calcitonin and CEA.

The ideal approach to prevent inter- and intra-laboratory variability is standardization[1]. This requires reference materials that are readily available and can be used for ongoing quality assurance testing. When standardization cannot be achieved, harmonization of test results can be achieved by overcoming assay-specific biases using attempts to recalibrate all methods to a common range.

STANDARDIZATION

The term "standardization" is used to describe the process by which comparable results are obtained by having each laboratory's method of calibration traceable to a reference measurement procedure. This requires 1) a clearly defined analyte and 2) a reference measurement with performance characteristics that can be defined using the International System of Units [Systèm International (SI)]. Standardization has been achieved for fT4[2,3]. However it cannot be achieved for many analytes despite the availability of reference materials such as recombinant human TSH.

HARMONIZATION

When unable to standardize tests as described above, laboratories can attempt to obtain agreement among measurement procedures by "harmonization" of testing using a reference system consisting of methods and materials that are not traceable to the SI but are agreed upon to act as references. This can involve a single method, known as a "designated comparison method", different methods that assign an "all-methods mean" or what is also called the "all-method trimmed mean" or "all-procedure trimmed mean". Reference materials can be prepared from purified biomarkers, a set of single-donor blood materials, or pooled patient samples. In special cases, a manufacturer's calibrator can be designated as a reference material.

STUDIES ON THYROID TESTING

The prevalence of thyroid disease and the frequency of testing required for patients with thyroid disorders led to many reports of discrepancies in this field. To address the issues of standardization and harmonization of common thyroid function tests, in 2005 the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) created the Working Group for Standardization of Thyroid Function Tests (WG-STFT), reporting to the IFCC Committee for Standardization of Thyroid Function Tests (C-STFT). The goal was to achieve equivalence of laboratory testing for total and free thyroid hormones, T3 and T4 as well as TSH. The committee has established a conventional reference measurement procedure for free thyroxine (fT4) and an approach to harmonization of results for TSH.

For standardization, the requirement for a standard with known SI units was available for total T4 and total T3[4]. However this is not the case for free thyroid hormones and TSH. For fT4, an IFCC-approved international conventional reference measurement procedure (cRMP)

was developed based on equilibrium dialysis isotope dilution-liquid chromatography-tandem mass spectrometry (ED ID-LC/tandem MS)[5]. Because of the complexity of TSH, with its variable glycosylation and the inherent difficulties in TSH-related and TSH-unrelated specificity problems, no RMP has yet been developed, therefore the approach has been to use statistical alternatives for 'harmonization' of test results. This has been successful in a number of institutions using common external quality assessment studies[6,7].

At this point, there has been little progress in standardization and/or harmonization of testing for other thyroid-specific analytes. For patients with autoimmune thyroid disease or thyroid cancer, measurements of thyroglobulin and anti-thyroid antibodies remain a problem due to significance inter-and intra-laboratory variability. The use of different methodologies in different laboratories poses a challenge when following a given patient over time, however, they provide an option when issues arise that may be due to method-specific interferences; for example, interfering antibodies may be a problem using one assay in a given lab, but not with another method employed at a different lab, so that testing in different systems can clarify the problem and offer the correct answer.

The Partnership for the Accurate Testing of Hormones (PATH) (http://www.hormoneassays.org) is an initiative by the Endocrine Society with representatives from a number of partner organizations including the ATA. The mission of this organization is to advance the development of standardized hormone assays that are traceable to a single higher order reference material and method (gold standard), and to advocate for the universal adoption of these assays in medical practice and research. Hormones currently standardized include testosterone, estradiol and 25-vitamin D. Standardization programs in development include free T4, TSH as well as free testosterone and PTH.

CONCLUSIONS

The goal of standardization and harmonization is to make the results of each thyroid hormone assay method interchangeable, so that—for example—aliquots of a serum sample in which TSH is measured give identical results independent of laboratory equipment, personnel, and environment and assay method. Standardization and harmonization of testing has immediate and obvious benefits. It is critical for surveillance of individual patients who require ongoing testing to monitor progression of disease and response to treatment. It is important to be able to obtain comparable laboratory data at the population level, for large scale studies. The ability to standardize or harmonize testing would allow a significant reduction in the need for repeat testing, and would therefore increase confidence in patient care. Importantly, evidence-based practice guidelines offer recommendations that are based on reliable and reproducible test results that must be available to those using the guidelines.

Despite the attempts of laboratories to standardize and harmonize testing methodologies and reference ranges, other variables affect individual test results as discussed in the accompanying document "accuracy and reproducibility". Sample-related effects remain as the most common causes of error or misinformation, mainly regarding immunoassay methodologies.

The impact of standardization and harmonization is obvious but the actual implementation requires consensus on methodologies, participation by vendors of testing platforms and reagents, as well as funding for the research that is required. These are not trivial issues and will become more important as technology moves to point-of-care testing. Further studies are necessary to determine whether standardization and harmonization of thyroid specific laboratory testing is truly possible[8].

REFERENCES

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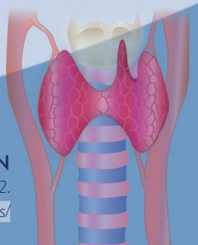

FURTHER INFORMATION

For more information on the survey findings, see *Thyroid, Vol. 27, No. 12.* https://www.thyroid.org/professionals/ata-publications/