Section 4. The Importance of the Laboratory – Physician Interface

Physicians need quality laboratory support for the accurate diagnosis and cost-effective management of patients with thyroid disorders. Laboratories need to offer analytical methods that are both diagnostically accurate and cost effective. These latter qualities are sometimes in conflict. Cost-effectiveness and quality care require that the laboratory serve not only the needs of the majority, but also meet the needs of the minority of patients who have unusual thyroid problems that challenge the diagnostic accuracy of the different thyroid tests available. Most studies on "cost effectiveness" fail to take into account the human and financial costs resulting from inappropriate management, needless duplication of effort and the unnecessary testing of patients with unusual thyroid disease presentations. These atypical presentations account for a disproportionately large expenditure of laboratory resources to come up with the correct diagnosis *(191)*. Some of these unusual presentations include: binding protein abnormalities that affect the FT4 estimate tests; the presence of Tg autoantibodies that interfere with serum Tg measurements; medications that compromise the in vivo and in vitro metabolism of thyroid hormones and severe forms of NTI that have a myriad of effects on thyroid test results.

Guideline 75. For Laboratories and Physicians

- It is essential that clinical laboratory scientists develop an active collaboration with the physicians using their laboratory services in order to select thyroid tests with the most appropriate characteristics to serve the patient population in question.
- An active laboratory-physician interface ensures that high quality, cost-effective assays are used in a logical sequence, to assess abnormal thyroid disease presentations and to investigate discordant thyroid test results.

It is essential that clinical laboratory scientists develop an active collaboration with physicians using their laboratory services and to select thyroid tests with appropriate characteristics to serve the patient population in question. For instance, the effect of nonthyroidal illness (NTI) on the FT4 method is not as important if the laboratory serves primarily an ambulatory patient population.

In contrast, it is very important for a hospital laboratory to accurately exclude thyroid dysfunction in sick hospitalized patients. Drugs and other interferences can affect the interpretation of more than 10% of laboratory results in general, and thyroid testing is no exception *(67,68,98)*. It follows that discordant thyroid results are often encountered in clinical practice. These discordant thyroid test results need to be interpreted with considerable care using a collaborative approach between the clinical laboratory scientist who generates the thyroid test result and the physician who manages the patient with suspected or established thyroid disease.

A. What Physicians Should Expect from Their Clinical Laboratory

Physicians depend on the laboratory to provide accurate test results and to help investigate discordant results, whether the tests are performed locally or by a reference laboratory. It is particularly important that the laboratory provide readily available data on drug interactions, reference intervals, functional sensitivities and detection limits as well as interferences that affect the methods in use. The laboratory should avoid frequent or unannounced changes in assay methods and interact closely with physicians before a change in a thyroid method is initiated. The laboratory should also be prepared to collaborate with physicians to develop clinical validation data with the implementation of any new method, as well as provide data showing a favorable relationship between the old and the proposed new test method as well as provide a conversion factor, if required. The diagnostic value and cost-savings of reflex testing strategies (i.e. adding FT3 when FT4 is high, or FT4 when TSH is abnormal) are usually site-specific *(495)*. In the United States, laboratories by law can only implement reflex-testing after consultation with the physicians using the laboratory.

Physicians should expect their clinical laboratory to establish a relationship with a reference laboratory and/or another local laboratory that performs thyroid testing by a different manufacturer's methods. Re-measurement of the specimen by an alternative method is the cornerstone of investigating whether a discordant result is caused by a technical problem, an interfering substance in the specimen or a rare clinical condition (Guideline 7

and Table 1).

Guideline 76. Patients "Bill of Rights"

- Physicians should have the right to send specimens for testing to non-contracted laboratories when they can show that the contracted laboratory thyroid test results are not diagnostically valid or relevant.
- Physicians should have the right to request their laboratory to send a specimen to another laboratory for testing by a different manufacturer's method if the test results are in disagreement with the clinical presentation.

The laboratory should establish and maintain an active relationship with specialized reference laboratories to ensure the availability of high-quality specialized thyroid tests. These specialized tests may include assays for Tg, TPOAb and TRAb tests. In addition, a reference laboratory offering FT4 measurements using a physical separation technique such as equilibrium dialysis should be available. The use of equilibrium dialysis for FT4 testing may be necessary under special circumstances for diagnosing thyroid disease in select patients with thyroid hormone binding protein abnormalities that interfere with the diagnostic accuracy of the automated FT4 estimate test performed in most clinical laboratories. In rare cases, it may be necessary to collaborate with a molecular diagnostic laboratory that has the expertise to identify genetic mutations characteristic of thyroid hormone resistance or medullary thyroid disease.

As shown in Table 1 and Figure 11, a number of clinical conditions, medications and specimen interferences can give rise to a diagnostically inaccurate test result that has the potential to prompt excess testing, inappropriate treatment, or in the case of central hypothyroidism mask the need for treatment. Some of the misinterpretations that can lead to serious errors are listed in Guideline 79.

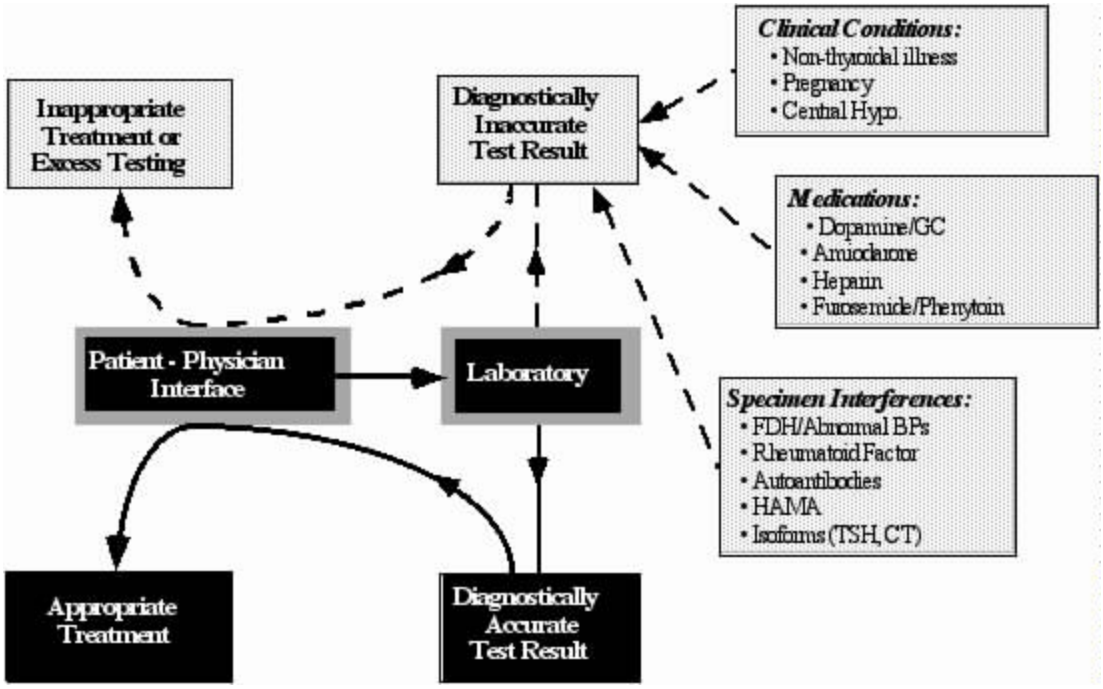

Fig 11. Consequences of Diagnostically Inaccurate Thyroid Tests

Manufacturers have the responsibility to thoroughly evaluate their methods and cooperate closely with laboratories using their products. Specifically, manufacturers should immediately inform all users of reagent problems that develop or method interferences when known and make recommendations as to how to minimize

the clinical impact of the problem. They should refrain from changing the composition of assay kits, even if the goal is to minimize interference, without informing customers and allowing sufficient time to perform correlation studies with the previous method. If the procedure has to be changed this should be indicated on the label of the kit i.e. by a version number.

Guideline 77. For Manufacturers

Manufacturers should cooperate closely with laboratories using their products. Manufacturers should:

- Rapidly inform all users of reagent problems and method interferences and recommend how to minimize their clinical impact.
- The composition of assay kits should not be changed, even if the goal is to reduce interference, without first informing customers. If the procedure has to be changed, the change should be indicated on the label of the kit (i.e. by a version number).

B. What Laboratories Should Expect of Physicians

Clinical laboratory scientists should ideally expect physicians to provide relevant clinical information with the submission of the test specimen and have a realistic understanding of the limitations of thyroid tests. For example, in some conditions, the physician should appreciate that the immunologic and biologic activity of TSH may be disconnected when patients have central hypothyroidism. This can result from pituitary dysfunction in which the immunoreactive form of TSH has impaired bioactivity *(197,238)*.

Guideline 78. For Laboratories

- Every clinical laboratory should develop a relationship with another laboratory that uses a different manufacturer's method. Re-measurement of specimens with discordant results by an alternative method is the cornerstone of investigating whether a discordant result is caused by an interfering substance present in the specimen or as a result of "true" disease (Table 1).
- Laboratories should be able to provide physicians with the details of the thyroid method principles underpinning the test being used together with functional sensitivity, between-run precision, interferences and any bias relative to the method or other methods, and whether the tests are performed locally or sent to a reference laboratory.

Guideline 79. Misinterpretations that Can Lead to Serious Errors

When physicians or laboratorians are not aware of the limitations of test methods, serious medical errors can result:

- Inappropriate thyroid ablation because high thyroid hormone levels were reported as a result of FDH, the presence of thyroid hormone autoantibodies or thyroid hormone resistance.
- A missed diagnosis of T3-toxicosis in a frail elderly patient with NTI.
- Inappropriate treatment of a hospitalized patient for hypo- or hyperthyroidism on the basis of abnormal thyroid tests caused by NTI or a drug-related interference.
- A missed diagnosis of central hypothyroidism because the immunoreactive TSH level was reported as normal due to the measurement of biologically inactive TSH isoforms.
- Failure to recognize recurrent or metastatic disease in a thyroid cancer patient because serum Tg was inappropriately low or undetectable due to TgAb interference or a "hook" effect with an IMA measurement.
- Inappropriate treatment for DTC on the basis of an abnormally elevated serum Tg caused by TgAb interference with a Tg RIA method.
- Failure to recognize that neonatal thyrotoxicosis can be masked by transplacental passage of antithyroid drugs given to the mother for Graves' disease.

The physician should understand that anomalous laboratory thyroid test results can occur with certain medications and that the diagnostic accuracy of thyroid tests used for patients with NTI is method dependent. Without clinical feedback, it is not possible for the laboratory to appreciate the consequences of a diagnostic error *(191)*. Misinterpretation of test results, as a consequence of a transient disequilibrium between serum TSH and FT4 following recent therapy for hypo-or hyperthyroidism can have significant consequences.

Without a strong, collegial laboratory-physician interface, the quality of laboratory support will undoubtedly be suboptimal. This is especially true in countries like the United States where laboratories rarely receive relevant clinical and medication information on the paperwork that accompanies the specimen. The inability of the laboratory to perform the final "sanity check" on the reported result(s) – i.e. relate the result to the patient's clinical and medication history, can lead to errors, especially when physicians are unfamiliar with the technical limitations and interferences affecting the test.